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With International Abstracts of Surgery

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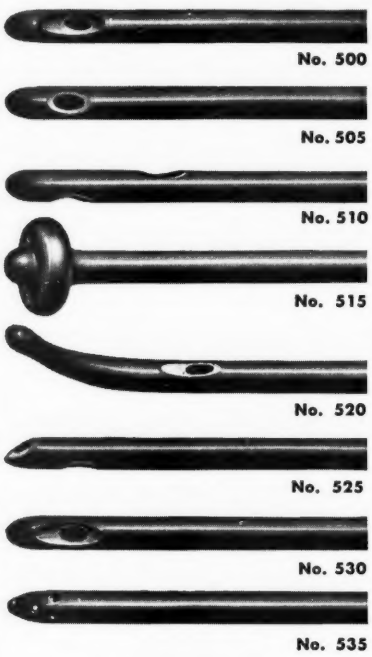

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A GOLDEN ANNIVERSARY

1905-1955

IN DECEMBER OF 1904, Franklin H. Martin invited four of the young men who had been associated with him in their surgical training to his home at 3210 Lake Park Avenue and, with the enthusiasm which only he could engender when he launched on a selling proposition, enlisted their aid in the organization and publication of a new surgical journal. Allen Kanavel, Frederick Besley, William Cubbins, and John Hollister had served as his surgical assistants and each estimated their chief and reacted to his imaginative genius in their individual ways. Nevertheless, their response was unanimous in the 500 dollar contributions which they made to the investment. Forty-nine per cent of the stock of the Surgical Publishing Company was distributed to his young associates and the controlling interest kept by Martin and his wife.

The interest of the R. R. Donnelley & Sons Company was enlisted in the publishing venture through the golfing friendship which existed at the Midlothian Club between Franklin Martin and Ted Donnelley. That interest has never wavered throughout 50 years and in spite of obstacles which naturally arise in the printing business, the blue journal of surgery has never failed to be issued on the first day of each month, though larger and more profitable magazines published by this great

A Golden Anniversary

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has endured for fifty years

firm have been late in the mails. Mr. Herbert P. Zimmermann's affection for the journal has been as great as his predecessors' and this has been transmitted to every member of the staff of the company so that a personal interest which goes far beyond the bounds of a business relationship is responsible for the progressive changes in paper texture, typography, and reproductions which have benefited SURGERY, GYNECOLOGY AND OBSTETRICS. We are proud and thankful that this important printing organization has always regarded this journal as its baby for whom it has a parental, protective affection.

Few enthusiastic, imaginative men have the ability to carry out their ideas into action smoothly and efficiently. Most of them need a partner, often silent, unselfish, and without ambition, to receive public credit for his deeds. In modern days these individuals have become popularly known as "hatchet men." They usually have an effect upon the more volatile half of the partnership like the governor on a stationary engine. Allen Kanavel was named as the Associate Editor while Martin designated himself the Managing Editor. From the first number which appeared July 1, 1905 until his death Kanavel, a practicing surgeon, was responsible for the editorial policies of the journal. This was the principal requirement which Martin wished the

The first announcement as to "Surgery, Gynecology and Obstetrics" was made to the general profession as follows.

"General Policy:

"Surgery, Gynecology and Obstetrics is in the hands of those who have for its development the highest ideals. The editorial staff must be the guarantee of its ethical and scientific standards. The business management is determined to make it a magazine which as a product of illustrated book-making shall be, adequate to its purposes, and artistic in appearance. Its commercial transactions will be based on business principles

"Literary Scope

"The journal will contain a wide survey of the Surgery, Gynecology and Obstetrics of the world.

1. Original articles upon practical, experimental, and statistical subjects will be judicially selected from all available sources and will constitute a major portion of the magazine.

2 Comprehensive original abstracts from local and foreign journals will form another important department

3 New books will be noticed and those deserving consideration will be thoroughly and carefully reviewed

4 Live subjects will be considered editorially The editorials will be written by masters who will be selected because of their fitness to speak on the subject under consideration, and such editorial will be, as a rule, signed.

5. Society reports will be a conspicuous feature of the journal. The larger societies at home and abroad will be thoroughly reported each month with adequate stenographic reports of discussions and abstracts of papers when the papers themselves are not published in full.

Editor to possess and he insisted upon it in planning the organization of SURGERY, GYNECOLOGY AND OBSTETRICS. This viewpoint was probably based upon the unpleasant experiences he had had when he submitted his own manuscripts to the "academic" editors of medical journals financed by commercial interests.

At Christmas 1906, a leather bound copy of the first number of the journal was presented to their friend, Dr. Martin, by three of his surgical pupils—Besley, Kanavel, and Richter. Beginning with a subscription list of about 600, the number had grown steadily in 18 months to reach 2,800 paying subscribers. The size of the journal had increased from 96 to 144 pages and the quality of the contributions developed in like proportion. The bottom of the barrel had to be scraped for manuscripts to fill the journal only for the second number when Kanavel removed from his desk drawer his own manuscript, "Acute Phlegmons of the Hand" which described the basic experiments for his classic monograph, *Infections of the Hand*. In the second number for the first time in a surgical journal, Donnelley's art department produced one of Max Brödel's colored illustrations by a four-color process.

Kanavel's longhand written copy of the first announcement of the new journal was a part of the presentation copy. These policies were clearly stated by Allen Kanavel and were inculcated in his pupils and the staff of the journal by his gentle methods of repetition and emphasis. He initiated and encouraged the addition of features which provided a flavor to the journal unusual in medical scientific periodicals.

The first announcement as to SURGERY, GYNECOLOGY AND OBSTETRICS was made to the general profession as follows:

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"Editorial Policy

"The editorial policy of the journal will be unique, as it contemplates the editing of the magazine by practical men of authority in their respective specialties. This will be accomplished by a systematic division of labor, making it possible for each man to do a small but definite and important part of the whole. This eliminates the figure-heads and will stamp with authority the contents of the journal

"Financial

"The journal is financed by a stock company of Chicago physicians, organized for its publication. It has no connection with any other commercial enterprise, but is published solely in the interests of the medical profession

"The Journal

In construction the journal will represent

"the very highest class of magazine making. It will be printed upon high-grade enameled paper that it may show illustrations to the best possible advantage. Inserts of lithographic reproductions will be furnished when illustrations of value require them. Care will be observed to cultivate the use of high-grade illustrations for all important articles. The normal size and shape of the journal will be similar to that of the American Review of Reviews

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The surgical journal prospered and from its earnings came the financial support for the meeting of the Clinical Congress of Surgeons in London, which was followed by the founding of the American College of Surgeons. Following World War I, Dr. Martin retired from active surgical practice and devoted himself to the College and SURGERY, GYNECOLOGY AND OBSTETRICS, although he studiously avoided any participation on the editorial side. In 1924, the journal moved to its present quarters which were remodeled from the stables of the residence which occupied the corner of Rush and Erie Streets, and a second remodeling occurred in 1945.

In the late twenties, Dr. Martin purchased the shares of stock which had been issued to his young associates at the beginning of the venture and added a generous

The Growth of Surgery, Gynecology and Obstetrics

Beginning with a subscription list of approximately 600, the number has grown steadily until the present time when the rolls show over 2800 paying subscribers, while less than a hundred have discontinued. Meanwhile the scope of the journal has been constantly broadened. From an early average of 96 pages it has increased to 1140 in the last Volume

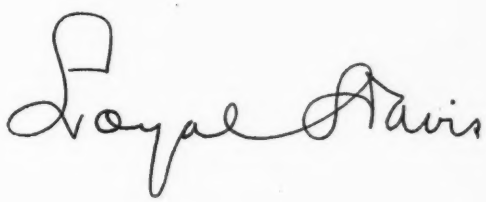
The Quality of the contributions has developed in like proportion. Over half the scientific articles pertaining to the three specialties which have been published during the last year can be found in its pages. While many high class monographs from foreign pens have been received. Practially every surgeon in the United States has demonstrated his confidence in the magazine by submitting articles. The special editions have familiarized the younger generation of scientific men in the Medical schools with value of the publication as a repository for their articles

At the end of the first year it was deemed advisable to increase the capital stock to $50,000. which furnishes ample support and insures the stability and permanence of the journal With an income, after a year and a half sufficient for the running expenses and a normal growth continueing there can be no doubt but that Surgery, Gynecology and Obstetrics will become a perpetual monument to the genius of its founder.

Allen B Kanavel

bonus. All of the shares of the Surgical Publishing Company thus became the property of Dr. and Mrs. Martin and he received an income from the earnings of the journal as its Managing Editor. Upon his death in 1935, Mrs. Martin alone owned the stock of the company and her annual income as President was the major security willed her by her husband. The net earnings had always constituted a reserve fund, one-half of which was used by Mrs. Martin to add to the annuity programs, which Dr. Martin had instituted, of those loyal staff members who had been with the journal since the appearance of the first number. At Mrs. Martin's death the shares and reserve of the Surgical Publishing Company became the sole property of the American College of Surgeons by the terms of Dr. Martin's will. Later, the Franklin H. Martin Memorial Foundation was created to effect the use of the earnings of the journal for the educational purposes of the College. A Board of Directors elected by the Regents of the College annually and an Administrative Board, consisting of the Editor, the General Manager, and the Comptroller of the College, administer the affairs of SURGERY, GYNECOLOGY AND OBSTETRICS.

The editorial policies and aims set forth by Allen Kanavel have been modified only slightly but in principle have never been changed. SURGERY, GYNECOLOGY AND OBSTETRICS remains a forum wherein the views of men interested in making contributions to the progress of surgery, after careful and painstaking investigations, experiments, and evaluations, may be published. It has always been and remains the aim of the staff and the Donnelley Company to present the material in the most artistic and accurate manner possible, and to this end the journal continues to have a staff whose affection and loyalty never waver. These three ingredients have been responsible for the success of SURGERY, GYNECOLOGY AND OBSTETRICS and the Editors gratefully and respectfully salute them.



AN OLD SURGEON VIEWS THE SURGERY OF TODAY

ALLEN O. WHIPPLE, M.D., Princeton, New Jersey

THE LAST SEVENTY YEARS in this country have been a period of amazing developments, unparalleled in the history of civilization. During this time we have seen the introduction of the automobile, the airplane, the cinemascope, radio and television, and lastly, to the danger of all of us, the atomic bomb. Today we travel on air and in the air.

But in addition to the inventions that have increased the tempo of our very existence, advances in medical science have been equally amazing. During this period of 70 years antitoxins, antisera, the x-ray, chemotherapy, and more recently the antibiotics—these, to mention a few of the advances in diagnosis and therapy—have prolonged the life expectancy of our people to the point that the degenerative changes of old age have made geriatrics one of the most important of our problems in medicine and sociology.

To be more specific, in this discussion of what an old surgeon sees in present day surgery I shall call attention to the advances which I have observed in dealing with surgical problems. During the latter part of the last century and the first part of the present century, American surgeons were especially interested in developing techniques to deal with the invasion of new areas in the expanding fields of surgery, such as the abdomen, the chest, and the head. The lack of adequate anesthesia and the hazards of that which was in use, together with the danger from shock and hemorrhage, as well as the example of European surgeons, made speed the yardstick and the clock the measure of the surgeon's competence. This encouraged showmanship and exhibitionism in many of the surgical amphitheaters of that time.

When I began the study of medicine in 1904, the change in emphasis from anatomy to pathology in the preparation for surgery was evident. But the recognition of physiology as the important discipline in the understanding of the functions of the various systems, and of maintaining them, did not gain much recognition among surgeons until World War I, when the study of shock and hemorrhage, by Cannon and other investigators, emphasized the role of maintaining blood volume and blood pressure.

Evarts Graham, Chairman of the Empyema Commission, and his associates demonstrated the importance of understanding pulmonary and thoracic function in their studies of streptococcus empyema during the influenza epidemic in our troops of that war. He was one of the first American surgeons to abandon surgery, after an internship, to study chemistry for 3 years in order to get a better understanding of the physiology and chemistry of surgical problems. Since then his example has resulted in the training of many of our leading young surgeons in chemistry, physiology, and bacteriology in relation to surgical lesions.

The factors which have increased the safety of surgery and widened the extent and radical character of operations in the various systems may be summarized as follows:

1. Anesthesia. In all its modalities—general inhalational, regional, local, spinal, intravenous, and hypothermic—advances have been so rapid that it is difficult to evaluate

them. But anesthetics have been used with so many preoperative, operative, and postoperative sedatives and narcotics that the combinations have resulted in too many complications during and after operation. They are being blamed for the unquestionable increase in the incidence of cardiac arrest which is being reported in recent years.

However, it must be said that the training of physician anesthesiologists in our better clinics has been of the greatest help to the surgeons in carrying out their extensive operations and in maintaining the proper respiratory and vascular balance of the patient. Some of the newer methods, such as hypothermia, are still in the experimental stage but in the hands of competent surgeons, especially in the field of cardiac surgery, give promise of success.

2. Blood transfusion. The establishment of adequate blood banks in so many of our hospitals and the better understanding of blood grouping and matching have made possible major surgery which previously, because of shock and hemorrhage, had been considered too hazardous. Maintenance of blood volume and blood pressure is essential in the prevention of shock, and, if present, in its treatment. However, the repeated transfusion of blood from different donors carries with it the danger of homologous serum reactions with liver damage.

3. Maintenance of protein, fluid, and electrolyte balance. The better appreciation of this factor has resulted in great advances in the preoperative, operative, and postoperative care of patients, as well as in the prevention of the syndromes which result from such imbalances that were not diagnosed in the past. The recent work done by our younger surgeons, trained in the basic sciences of chemistry and physiology, in the understanding of cell volume and electrolyte exchange has been a great contribution and has raised surgery from being considered a manual performance to a major branch of scientific therapy, in the eyes of medical and premedical confreres.

4. The antibiotics. During the past 10 years the earlier bacteriolytic and bacteriostatic chemical sulfonamide compounds have given way to the rapidly increasing antibiotic group, now largely derived from the fungi. These are more effective not only in the coccus but in the bacillary variety of organisms. So effective are a number of these mycin preparations that not only are blood stream infections controlled but localized infections as well. One no longer has the cold dread of septicemia, empyema, meningitis, and peritonitis which we had 20 years ago.

However, the indiscriminate administration of large doses of the antibiotics in shotgun fashion, without first determining the susceptibility of the invading organism to one or more of the antibiotics, is both stupid and unintelligent and is to be condemned. It must be said also that the use of these antibiotics has compromised diagnostic effort and clouded surgical judgment. I have heard of a hospital in one of our large cities, where the patient with a temperature on admission is given a shotgun dose of antibiotics. If his temperature does not subside within 24 hours a history is taken and a physical examination made! The clouding of surgical judgment is seen in the delay in early operation for acute appendicitis, perforated peptic ulcer, and intestinal leakage and gangrene. Rather than using antibiotics after evacuating the pus and preventing the spread of the infection, too many surgeons, as well as general practitioners, delay drainage of an abscess until they have tried one or more of the

antibiotics. Furthermore, the use of these mycins has made some of the older as well as the younger surgeons careless and sloppy in the handling of clean and contaminated wounds, trusting to the antibiotics to prevent wound infection. This is bad surgery.

5. The improvement of surgical hospital facilities. To the American College of Surgeons, in its Hospital Standardization Program, belongs the credit of improving the surgical facilities in our hospitals throughout the country as well as of requiring high standards in the conduct of the surgical services in these hospitals. These together with the improvements in the roads and transportation facilities have brought the public in rural areas within easy access of adequate hospital care and have made emergency treatment much more available than was the case 20 years ago.

6. The educational program of the American College of Surgeons. Since its organization the College has conducted such a program, which has improved in quantity and quality as time has gone on, especially in recent years with the introduction of the Panel Discussions. These have been designed to give the younger group of surgeons the opportunity of presenting worthwhile research in surgical and allied problems, and of having them discussed by their peers and by their older mentors. This program provides the opportunity to surgeons in great areas outside of metropolitan districts to hear reports on recent developments and to see new appliances and instruments in new fields of surgery.

7. The recognition of safe, deliberate operative technique. With the improvements in anesthesia, blood volume maintenance, and shock prevention, careful and deliberate operations with minimum tissue trauma and the use of fine nonabsorbable suture material are being used by an increasing number of surgeons and by the great majority of our resident trained surgeons in all parts of this country. Halsted's influence in this field cannot be overemphasized.

To an old surgeon who has had the experience in his earlier years of operating in hospitals and homes, before and after the long term program of residency training was recognized and accepted, this program has been the most effective factor in improving the surgery of today and in developing the outstanding ability of our younger generation of surgeons.

William S. Halsted, the first Professor of Surgery at the Johns Hopkins Medical School, must be acclaimed one of the greatest influences in advancing American surgery not only because of his original contributions to the surgery of the breast, the thyroid, hernia, and his meticulous technique in wound repair but particularly because of his initiation and development of the residency training program. Following his early career as a brilliant young surgeon in New York City, Halsted withdrew from surgery for 3 years before he was appointed to the professorship in Baltimore. During this period of enforced contemplation he developed his philosophy of meticulous safe surgery as well as his program of surgical residency training. During the next 20 years he was more or less a lone worker in these fields, but his carefully trained residents were so outstanding in their operative skill and in their original research that many of them were appointed to important professorships in the medical schools of this country. It has been most interesting to note the trend toward the careful safe surgery of the Halsted school in recent years as well as the adoption of residency training in the leading surgical clinics of the United States and Canada.

But there are other and more immediate reasons than Halsted's influence in the acceptance of the residency training program. By 1935 the ability of well trained residents in our leading surgical clinics had become so evident that it became mandatory to recognize their competence over the incompetence of men doing surgery following an internship, or none. For this reason the American Surgical Association appointed a committee of 6 of its members to study this problem and to report on it at its next meeting. As a result of the recommendations an examining and qualifying American Board of General Surgery was organized in 1937. This was made up of 13 surgeons—3 from the American Surgical Association, 3 from the American College of Surgeons, 3 from the Surgical Section of the American Medical Association, and 1 member each from the Western Surgical, the Pacific Coast Surgical, the New England Surgical and the Southern Surgical Association. This Board was approved by the Advisory Board of Medical Specialties and the Council of Medical Education of the American Medical Association and took its place with the specialty boards in other fields of medicine.

As a result of the high standing in the qualifying examinations of the American Board of Surgery by the well trained residents, General Rankin of the Army Medical Corps gave higher rank to these resident trained men in his appointments to active duty during World War II. The younger officers of lower rank, many of them with only a 9 months' internship after graduating from medical schools, quickly appreciated the greater skill and better surgical judgment of the resident trained surgeons and were convinced of the need for such training if they were to do surgery.

A final urge to get residencies came after the war with the reorganization of the Medical Department of the Veterans Administration, when the appointments as attending men to the surgical services in those hospitals was limited to surgeons who had had residency training and had been qualified by the American Board of Surgery. This together with the policy of many of the civilian hospitals, whose boards had come to appreciate the advantage to their patients and their staffs of appointing surgeons who had been qualified by the American Board of Surgery, increased the demand for residency training that far exceeded the number of hospitals that were qualified to give such training.

As a result of these several factors which have been discussed, American surgery has made amazing progress in many fields—abdominal, pulmonary and thoracic, cardiovascular, neurologic, endocrinologic, plastic, and orthopedic. When I began my training such procedures as pneumonectomy, total gastric, pancreatic, and colon resections, mitral and aortic valvulotomies, resections of aortic stenosis and aortic aneurysms with aortic grafts or transplants, portacaval anastomoses, excisions of parathyroid and pancreatic adenomas for hypersecretion, to name a few—were never heard of or never attempted. Today the teamwork in the care of the severely burned and of severely injured patients in the too common motor accidents is saving an increasing number of lives. The use of grafts from bone, eye, and vascular banks in providing replacement material is another important development.

Yet, with all the advances which have been made in the past half century, there still remain problems that need the advice of the older more experienced surgeons and their guidance in the clinics where residents are being trained. Sound judgment comes with experience

and proper conduct with integrity. Though technically many residents in their last year of training become as clever as their senior attending surgeons they have much to gain from them in understanding when to operate and when not to, what, when, and how to tell patients unwelcome news—especially the families—how far to go and when to stop in operating for cancer. The surgical chief and his staff of associates should take time and show a real interest in making rounds with his residents, and should assist them in some of their difficult operations. For it is in these close contacts that the older surgeon's greater experience can be shared with his resident staff to their great benefit.

It is in the field of radical surgery for cancer that this relation can be most helpful. With the factors of safety which have been developed, the length of time taken and the amount of tissue that can be removed are not as important as the question, "How much will life mean to the patient after operation in terms of comfort and function?" The presence of intolerable pain and vesicovaginal and rectovaginal fistulas in a woman with grade III uterine cancer is justification for pelvic exenteration but not if, on exploration, the peritoneum and intestinal tract are invaded by the cancer. There comes a time when patients should be allowed to die comfortably. There is a fundamental difference between controlled sedation and euthanasia.

Finally, the example of the surgical chief and his associates in their integrity and professional conduct and in their doing honest surgery as well as in their relations with their confreres in medicine and the other specialties, including their attitude toward the division of fees, is of paramount importance in shaping the character and future conduct of the residents. This relationship is well illustrated in the operating room. The surgical team is like a quartet or quintet in chamber music, in its tempos varying from allegro to adagio to scherzo and finale, but maintaining harmony and without the presence of prima donnas.

This has been a great period of half a century in which to have lived and worked. It has been a great privilege to have been of some help to those who needed it, and to have known and been associated with so many good friends in and out of the surgical profession.

A YOUNGER SURGEON VIEWS THE SURGERY OF TOMORROW

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Throw away, in the first place, all ambition beyond that of doing the day's work well.—*Osler*

NO ONE HAS YET PREDICTED successfully the future of surgical developments for even short periods of time and it is reasonable to presume it cannot be done now. Its future is better served, "not by seeing what lies dimly in the distance, but by doing what lies clearly at hand." Nevertheless, in light of historical and recent accomplishments, it is obvious that surgery is as vigorous and stimulating as it has ever been and that its future is secure even though its course remains unknown.

FUTURE IN THE PAST

The outstanding feature pervading the history of surgery is its continued growth. This growth, however, has not always been steady or necessarily obvious. Upon many occasions in the past the horizons of surgery have been neither distant nor broad.

Certainly this was the most that could be said of the future of surgery in the middle of the twelfth century, when following the pronouncement of the Council of Tours, "Ecclesia abhorent a sanguine," the teaching of surgery was slowly discontinued from the medical curriculae throughout the major faculties of all Europe, beginning with the Faculty of Medicine at the University of Paris about 1170 A.D. The events to follow were those of contagion and blight. Within less than 75 years, all who worked with their hands were excluded from medical faculties, and those in pursuit of a surgical career were denied the educational opportunities of their day.

This unfortunate course of events was to affect the entire field of medicine—not just that of surgery alone. Its consequence is no better related than by Allbutt in 1904, then Regis Professor of Physic at Cambridge: "That in the truncation of medicine the physician lost not only nor chiefly a potent means of treatment, he lost thereby the inductive method; he lost the only laboratory at his service; he lost touch with facts; he deprived his brains of the co-operation of the subtlest machine in the world—the human hand, a machine which does far more than manufacture, which returns its benefits on the maker with usury, blessing both him that takes and him that gives."

This period in surgical history gives substance to the Hippocratic precept that, "Healing is a matter of time, but it is also a matter of opportunity."

There was little reason to envision great extensions of the horizons of surgery at the time of Paré or Felix, in the sixteenth and seventeenth centuries, although the era of the barber surgeon was about at its end. A century later, however, new vistas were clearly within the mind's eye of John Hunter and Astley Cooper, yet the great advances to be made possible through the development of anesthesia and antisepsis lay more than 50 years in the future.

The advent of anesthesia and the evolution of aseptic surgical principles are the greatest accomplishments surgery has yet made. These two discoveries enabled the rapid development of surgery within the regions of the abdomen, extremities, and neck. These were the opportunities of tomorrow nearly a century ago. They were quickly recognized and exploited by many surgeons, but particularly by Billroth, Kocher, Paul, Mikulicz, Miles, and Halsted. This was the beginning of the great era of technical surgery; an era that was well along before the first departments of physiology and biochemistry were established in the medical schools of this country. Its impact was legion, and soon the surgery of turbulence and threat, so vivid to the memory of Ephraim McDowell was to slip quietly into the past.

Surgical horizons at the beginning of the twentieth century extended rapidly into the fields of neurologic, thoracic, and cardiovascular disease. In recent decades the technology of these fields has grown to maturity and once again our attention can be focused upon more basic mechanisms of health and disease.

There is always a fascination about pioneering and about pioneers. The surgeon who pioneers is no exception. His courage and fortitude are not necessarily evident when examined by another generation, for in the absence of the historian's approach it is not likely that his life will be viewed in the reconstructed atmosphere which created the problems he encountered and upon which he worked; more often only portions of the general picture can be brought into sharp focus; the rest remains as shades of grey. That he, the surgeon of the past, was bold and resourceful there can be little doubt. Yet, the difficult operations which he first devised in his limited technical experience, rapidly gave way to the alacrity and finesse of the next generation of surgeons who now were better able to understand the disturbed physiology of the primary disease as well as that of the operation itself.

For the most part surgical technique has preceded surgical physiology. However, as the problems of physiology and biochemistry incident to the operative procedure become evident and their solutions evolve, many of the difficult technical details have been simplified. This will continue.

At a time when every cavity of the body has been laid bare in the course of the surgeon's daily routine, what then is the future of surgery?

Has not this branch of medicine already accomplished about all it can hope to achieve?

As long as problems in surgery remain unsolved, there is always a future. And there are in surgery unlimited numbers of problems; problems in surgical training and education, problems in diagnosis and patient care, in methods of practice, research and even in surgical technique. They are influenced by certain environmental factors, some of which are not surgical nor necessarily even scientific; thus, the total achievement for surgery of any particular period is the sum of progress along many facets of endeavor.

THE GIVE AND TAKE OF SURGERY

Any endeavor which has for its goal the relief of mankind from the diseases which beset him, must inevitably work for its own extinction, as progress is made. Thus far, however, progress in medical research has affected only the character of medical practice. It has enlarged rather than curtailed the scope of surgical activity. Yet, any loss to the thera-

peutics of medicine is welcomed as an advance, if it benefits the patient the physician must serve. In a few instances the net effect has been to change profoundly an entire field.

The advent of the antibiotics is perhaps the medical discovery which has most significantly altered the character and practice of medicine and surgery during the past 50 years. Its influence upon the future of pediatrics, infectious diseases in general, and those of the ear, nose, throat, and chest in particular is sufficient to give pause as to either the desirability or wisdom of the apparent seemingly never ending trend of subspecialization. The field of otolaryngology is especially threatened as its field of training was designed for the preantibiotic days; in general this specialty cannot be adapted to other types of surgical endeavor about the head and neck without fairly radical change in its basic program of training. Fortunately, steps are being taken to revise the field so that the skills peculiar to the otolaryngologist and still useful in other diseases will not disappear for the want of patients to be cared for or for students to be taught.

The plight of the otolaryngologist will not continue unique; other subspecialties may within our time be subject to a similar need for an increase in function rather than for their continued refinement until extinct. It is doubtful that the few millimeters' thickness of the diaphragm will continue long as a barrier sufficient to separate thoracic and general surgery once either of these fields is seriously curtailed. It is the qualifications of the surgeon that need to be highly specialized and refined—not his field of operation. His qualifications enable him to do more. Not less!

The surgery of infections in the past was often surgery of latent and serious complications. It was as frequently the surgery of reconstruction as it was the surgery of drainage. Antibiotics have largely prevented the surgical sequelae of infections. The need for surgery in the complications of venereal disease is largely gone. Chronic osteomyelitis, which engaged serious and studious attention as early as the time of Lister and as late as that of Phemister is rapidly disappearing from the surgical wards as better control of the acute phase is achieved with antibiotics and early surgical drainage. The nature and magnitude of the surgery of tuberculosis already has been altered to a remarkable extent by appropriate public health measures and intelligent use of the limited drugs currently at hand; a really effective antitubercular drug could well nigh abolish the need for surgery in this disease and who among us doubts that this day will come?

At the same time, the control of most common infections has given to surgery far more than it has taken away. First of all, the generous extension of life expectancy among the population at large has increased enormously the numbers whose surgery centers directly or indirectly about disorders of the aged. Foremost among these is the surgery for malignant disease to which the human population seems much more prone than was suspected when the life span was less than now. Control of many common infections has enabled the surgeon to operate in areas where postoperative infection was the anticipated rule and which frequently necessitated serious compromise or surgical abandonment. Surgery of the left colon, the upper stomach, the esophagus, and chest are but a few examples where antibiotics have enabled surgical extension in both malignant and benign disease. There is, however, much credit due in these patients to the intelligent transfusion of blood

and plasma, improvements in anesthesia, and preoperative and postoperative care. Together all of these measures account for and will continue to contribute to the over-all gains in surgery. The use of these principles must be extended into the large area of the surgery of trauma where they may often make primary surgery possible.

Cardiovascular surgery, whose infancy began in infants, seems destined to grow into all ages of life. Already it is being extended into the therapy of atherosclerosis in the aged —particularly of the great vessels and soon it will embark upon another area of the cardiologist—coronary arteries themselves.

PROBLEMS IN LEARNING SURGERY

Men are most apt to believe what they least understand.—*Montaigne*

No discussion of surgical horizons can long avoid problems in medical education. Some of these problems are peculiar to surgical education, but most are common to medical education as a whole. Careful scrutiny suggests that most of the difficulties center about the physician's education rather than his professional competence. The doctor today is highly skilled in his particular field of science and is able to bring to his patient the best his profession can offer.

The manner in which this education evolves raises several questions. Among these are: that half of the man's life expectancy is consumed in his training and education; that the education he receives prepares for little more than his professional life; that the costs are prohibitive and in consequence potential applicants for medicine are limited; and finally that the subject matter is too broad to be mastered without some tendency to specialize.

The learning process in surgery is a combination of training and education: training in the sense of habit, education in the sense of the balance struck between knowledge and wisdom. Goals in training can be reached relatively early; those in education are achieved relatively late. It is neither practical nor possible to describe all of the learning processes as either training or education for there is much overlap. The life of a surgeon is a mixture of art and science, seasoned in human experience: "It is in one way hard and in another way easy. For it is evident no one can master it fully nor miss it wholly. But each adds a little to our knowledge of nature. . . ."

Most professional educators believe the high degree of professional competence of today's doctor is accomplished at the expense of his cultural education. To a greater or lesser degree, this criticism may be correct; but wherein lies the blame? The doctor devoted 16 of his most formative years to the demands of general education before he arrived at the portals of medical school. During his 4 years of college he was subjected to the minimum science requirements established by the American Association of Medical Colleges which may or may not be modified to some extent by the individual school. While these requirements probably exceed those which are essential to the study of medicine, they are not much more than should be required in a well rounded curriculum leading to the Bachelor of Arts degree in the humanities. However, the tendency is for the premedical student himself to pile one science course upon another without regard to the eventual outcome of his background in general education. Yet, his additional courses in science could be

allowed and without harm providing they were not permitted to displace his general education. The facts are that the doctor does not leave his medical school poorly educated in the humanities, he arrives from college that way. If general education is to be provided it must be achieved at and before the college level. This is therefore primarily a problem to be solved within the time and effort devoted to high school and college education. The medical school must be reserved for professional education and training. The medical student whose interest in other fields was not awakened earlier will not suddenly embark upon more general and cultural activities simply because he becomes a doctor.

Education at the medical school level suffers from important disorders, some of which are inconspicuous but few are inconsequential. The cost of medical education is the problem of the greatest concern today. So far as the future of medicine is concerned, however, the cost is perhaps least important. Medicine's essential role in society guarantees its future life, but not necessarily the fate of its soul. Its soul can be lost upon the battle grounds of cost. Yet, it is well within the grasp and responsibility of the profession to finance the major portion of tuition expense. This is an investment in the future that both doctor and patient can ill afford to lose. The solution to the cost of patient care is already self-evident and well along toward its goal, thanks only to the slow awakening of the doctor to his essential role. We nearly lost this one a decade and a half ago!

More significant than cost of medical education is its substance. The last serious evaluation of the medical curriculum was that which produced the Flexner report 45 years ago. The impact of this survey was enormous and it served its purpose well. But the continued influence of this report is one of default by medical education rather than from any omniscience and immortality inherent in the report. It was written at a time when the internship was optional and elected by few, when the residency program was little more than a dream, in a day when the specialist was occasionally self-made and more often self-declared, and when limited transportation centered the practice of medicine about the home.

Times have changed but not the medical curriculum!

For the most part the curriculum has grown without the particular guidance or necessary care essential to its equilibrium. We must begin again and anew to review the curriculum, stripping from it those courses acquired by custom rather than intent. We must re-examine without prejudice its basic structure and be willing to discard those parts not needed or outmoded. Before the whole is reassembled again, certain questions must be reviewed in the light of day—today's day. Foremost, what should be the role of the medical school in the field of medical education? How much more than a broad background in medical education should it attempt or is it able to provide? How much of the education and training should or could fall into the internship and residency training programs? Through the years, much of the effort and program of the medical school has been duplicated by the experience offered by the internship and residency programs. It would be surprising if a restudy of the medical curriculum and the postgraduate training hospital programs did not disclose at least a 25 per cent duplication of effort and time and that this could be discarded to the benefit of all. These are but some of the questions deserving of serious attention. They are important because the awarding of the degree of Doctor of Medicine

frequently represents less than 50 per cent of the time the medical student and young doctor must "serve" before he enters his practice. The postgraduate training period for some time has shown clear evidence of becoming one of attrition rather than training by precept. It can dull the imagination beyond response and even repair. The student cannot and should not be carried indefinitely before he tries his wings. He, not the medical school nor residency training program, is the master of his fate.

At the same time the residency program can and should be broadened in certain respects, especially in the fields of pathology, radiology, and clinical laboratory procedures—and without lengthening the period of training. The tendency is for these specialties to be separated more and more widely from the clinical training or practice of surgery. The surgeon becomes unnecessarily dependent upon his colleagues in many fields, particularly these. His colleagues cannot share his advantageous position in diagnosis; only he has the opportunity to inspect the pathology *in situ* and to validate, modify, or correct the preoperative impressions and contributions of the radiologist and pathologist as well as his own. Certainly the surgeon, more than most physicians, should be aware of his own limitations as well as those of his professional allies in the "hand maiden" specialties. Yet in the pursuit of his technical experience, the young surgeon too often surrenders his academic interest and intellectual curiosity to schools of manual training. Technical competence is essential to any surgeon: indeed, it is the *sine qua non*. It is assumed. But technique for technique's sake obscures many other facets of surgery, some of which are of equal or greater importance.

There is good reason to believe that the future of surgery and the future of physiology will run in parallel directions if, indeed, they do not actually merge at numerous points for several reasons. In the future, surgery will lean more heavily upon physiology. This need not prove awkward for it comes at a time when the classical physiologist is leaving the far from completed field of organ physiology in favor of cellular studies. If the surgeon is to learn more of organ physiology he is likely to be forced into the position of being his own teacher and of doing his own research. The migration will be for the biochemist to move into biophysics, the physiologist to become tomorrow's biochemist, and the surgeon to assume at least a dual role—that of the surgeon and the physiologist. The surgeon's technical skills fit him especially well for his new assignment.

These are all steps for the better. Fortunately, they come at a time when technical surgery is highly developed and when the advances to be made in surgery depend upon a greater knowledge of physiology, especially human physiology. This is a role the physiologist is less able to assume than the surgeon is able to adopt. Yet, none would deny that before this transition can be accomplished with satisfaction to all, the surgeon must be better prepared in general physiology. An appraisal of the programs of the Surgical Forums of the American College of Surgeons over the past dozen years indicates the magnitude of the strides made in this direction. At the same time, it is becoming increasingly clear that little is known of the physiology of man, and that many of our past views on general physiology may need serious revision in the light of the newly acquired facts that the surgeon is able to provide.

The future of surgery is bright indeed, but it is not free of growing pains.

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A COMPARISON OF VAGOTOMY AND GASTRIC RESECTION FOR GASTROJEJUNAL ULCERATION: A FOLLOW-UP STUDY OF 301 CASES

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THE TERMS "gastrojejunal ulcer," "stomal ulcer," "marginal ulcer," "postoperative jejunal ulcer," and "jejunal ulcer" are used more or less synonymously throughout the literature to designate recurrent peptic ulceration following some type of gastrojejunal anastomosis. For the purpose of this discussion we shall refer to these ulcers as gastrojejunal ulcers after gastroenterostomy and after gastric resection.

The majority of these ulcers involve the jejunum only, although at times they may include the site of the anastomosis.

Before the advent of vagotomy the treatment of gastrojejunal ulcer was fairly well standardized. Excision of the ulcer associated with high gastric resection was the procedure of choice. When gastrojejunal ulcer developed after partial gastric resection, the outlook was not too satisfactory, for re-resection was attended by an operative mortality rate of about 10 per cent and only about 50 per cent of patients so treated obtained a satisfactory result. By contrast the outlook for the patient with gastrojejunal ulcer after gastroenterostomy was very favorable because excision of the ulcer and high gastric resection gave excellent results in 85 to 90 per cent of the cases with an average operative mortality rate of 4.1 per cent.

With the advent of vagotomy the results of treatment of gastrojejunal ulcer developing after gastric resection have been improved and a considerable reduction in operative mortality rate has occurred. Because of these facts some surgeons, among them Crile and Brown, are now advocating vagotomy as the treatment of choice for all gastrojejunal ulcers including those which follow gastroenterostomy. This study was undertaken to compare the effectiveness of vagotomy with that of gastric resection in the management of gastrojejunal ulcer after gastroenterostomy and the effectiveness of vagotomy with and without gastric re-resection with that of

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gastric re-resection alone in the management of gastrojejunal ulcer after gastric resection.

We think this study is important and significant because it compares the results in two groups of cases treated by the same surgeons, over the same period of time, and under the same general conditions and shows the superiority of gastric resection over vagotomy in the surgical management of gastrojejunal ulcer after gastroenterostomy, while at the same time demonstrating the important role of vagotomy in the management of gastrojejunal ulcer after a partial gastric resection.

CASES STUDIED

Vagotomy in the treatment of gastrojejunal ulcer was first used at the Mayo Clinic in 1945. In the years 1945 to 1952 inclusive 617 operations were performed on 586 patients for gastrojejunal ulcer. One hundred forty-three of these operations consisted of vagotomy alone or combined with additional procedures, while 474 were operations in which vagotomy was not done. This latter group consisted primarily of gastric resection.

The 143 patients who had gastrojejunal ulcer treated by vagotomy make up the "vagotomy group." This group includes 118 patients on whom follow-up data were reported by Walters, Priestley, and Belding before the meeting of the American Medical Association in June, 1951, as well as those patients on whom operations have been done from that date through 1952. A group of 158 patients who had gastrojejunal ulcer treated by gastric resection or gastric re-resection during the same interval was studied also, and will be referred to as the "resection group." The "resection group" was selected by listing in ascending order the record numbers of the 474 patients who had operations other than vagotomy and then choosing every third case record. Should the record called indicate that an operation other than resection had been performed, then a record bearing the adjoining number was called until we had records of 158 cases of gastrojejunal ulcer in which gastric resection had been performed; these constitute the series included in the present study.

Since certain clinical features as well as the surgical management of gastrojejunal ulcers following gastroenterostomy and gastric resection differ, the 301 cases comprising this study were divided into two groups: 115 cases in which the gastrojejunal ulcer occurred after gastric resection, and 186 cases in which gastrojejunal ulcer occurred after gastroenterostomy. By analyzing certain clinical features of these two groups preoperatively and comparing them with the same features in the postoperative period we are able to arrive at some concrete evidence to support the conclusions of our follow-up study.

CLINICAL FEATURES

Etiology. Though gastrojejunal ulcers have been attributed to many causes such as nonabsorbable suture material, foci of infection, spasm, stasis, the mechanical or "jet effect" of a small stoma and many others by Benedict, Mayo, Wilke, Steinberg, Mann, Morton and others, it is now generally agreed that the cause of gastrojejunal ulcer is similar to that of duodenal ulcer whatever they may be and generally follows an operative procedure for duodenal ulcer. Gastrojejunal ulcers are rare after gastric resection for gastric ulcer, although Ransom reported an incidence of 3 per cent after such operations, Priestley and Gibson reported the antecedent lesion to be a gastric ulcer in 1.4 per cent of the 283 cases of gastrojejunal ulcer, which they studied.

In the present series of 301 cases the gastrojejunal ulcer followed operation for duodenal ulcer in 290 cases (96.3 per cent), gastric ulcer in 6 cases (2.0 per cent), and gastric and duodenal ulcer in 5 cases (1.7 per cent).

Incidence and interval between operations. Although the incidence of gastrojejunal ulcer following gastric resection is lower than the

incidence following a gastroenterostomy in the present study no attempt was made to determine this incidence. However, the mean interval between the previous operation of partial gastric resection in 115 cases and the operation for treatment of the gastrojejunal ulcer was 3.7 years, while in 186 cases of gastrojejunal ulcer following gastroenterostomy the mean interval was 11.2 years. It is obvious from these figures that to determine the incidence of gastrojejunal ulcer following either gastric resection or gastroenterostomy a long-term follow-up is necessary. This is particularly true after gastroenterostomy and probably explains why the incidence of gastrojejunal ulcer first reported was low, but has gradually increased as the time of follow-up increased.[1] Also this long interval between gastroenterostomy and the surgical treatment of a subsequent gastrojejunal ulcer will require a prolonged period for evaluation of vagotomy combined with gastroenterostomy in order to arrive at the incidence of gastrojejunal ulcer following this combined procedure and to determine whether the results are improved by the addition of vagotomy.

Age and sex. The mean age at the time of surgical treatment of gastrojejunal ulcers was 46.1 years for the 115 patients who had had gastric resection and 51.4 years for the 186 who had had gastroenterostomy.

Gastrojejunal ulcer, like duodenal ulcer, occurs predominately in men. In the present study of 301 patients, 274 (91 per cent) were men, while 27 (9 per cent) were women.

Previous operations for peptic ulcer. Seventy-eight of the 301 patients had 2 or more previous operations for peptic ulcer, while the remaining 223 had only one previous operation, either partial gastric resection or gastroenterostomy.

[1]We are well aware of the fact that these figures do not indicate the mean interval between the time of operation and the onset of recurring ulcerlike symptoms. Yet sometimes symptoms of recurring ulcer are not due to ulcer as determined at operation, and as will be shown there is a high incidence of error in the roentgenologic examination of patients with gastrojejunal ulcers.

TABLE I.—PREVIOUS OPERATIONS IN 46 CASES OF GASTROJEJUNAL ULCER AFTER GASTRIC RESECTION

Operation	*No.**
Partial gastric resection	46
Gastroenterostomy	28
Gastric re-resection	16
Surgical closure of perforated duodenal ulcer	12
Local operation on gastrojejunal ulcer	8
Vagotomy	4
Pyloroplasty	2
Excision of gastrojejunocolic fistula	2
Gastroenteric anastomosis taken down	2
Gastroenteric anastomosis taken down and new gastroenterostomy	2
Gastroenterostomy with enteroenterostomy	2
Devine exclusion operation	2
Closure of acute perforation of gastrojejunal ulcer	1
Gastric re-resection and vagotomy	1
Excision of gastrojejunal ulcer and Roux "Y" gastroenterostomy	1
Gastric resection with enteroenterostomy	1
Excision of gastrojejunocutaneous fistula	1
Exploration:—impossible to determine what was done	1

*Patients had more than 1 operation so that the total operations are greater than the number of patients.

Since by far the majority of these patients had their previous operations elsewhere, it was difficult at times to ascertain just what had been done, but by reviewing the histories, letters from the referring doctors and combining these with the findings in roentgenograms of the stomach and at the time of operation we were able to determine fairly accurately what had been done previously.

The 78 patients had undergone 206 previous operations for peptic ulcer, an average of 2.6 operations per patient. Since these operations had not cured the patient or had resulted in substituting a gastrojejunal ulcer for a previous duodenal ulcer, it seemed worth while to determine what these previous operations were. Forty-six of these patients who had undergone multiple operations had gastrojejunal ulcers after gastric resections. On these 46 patients 132 operations had been performed previously and these are tabulated in Table I.

Of the 186 patients in this study who had gastrojejunal ulcers after gastroenterostomy, 32 had undergone 74 previous operations for peptic ulcer. These operations are summarized in Table II.

Complications. The complications of gastrojejunal ulcer are perforation, gastrojejuno-

TABLE II.—PREVIOUS OPERATIONS IN 32 CASES OF GASTROJEJUNAL ULCER AFTER GASTROENTEROSTOMY

Operation	*No.**
Gastroenterostomy	32
Surgical closure of acutely perforated duodenal ulcer	18
Closure of acutely perforated gastrojejunal ulcer	6
Vagotomy	4
Excision of gastrojejunocolic fistula	4
Gastroenteric anastomosis taken down, new gastroenterostomy	3
Pyloroplasty	2
Excision of gastrojejunal ulcer	2
Gastroenteric anastomosis taken down, new gastroenterostomy and vagotomy	1
Closure of perforated gastric ulcer	1
Excision of gastrojejunocolic fistula and jejunojejunostomy	1

*Patients had more than 1 operation so that the total operations are greater than the number of patients.

colic fistula and hemorrhage. In this series of 301 patients only 2 were seen with an acute perforation, though a number gave a history of acute perforation which had been treated elsewhere.

Gastrojejunocolic fistula is the most serious complication of gastrojejunal ulcer, and the incidence has been variously reported as 8.7, 11.4, and 13.6 per cent by Judd, Priestley, and one of us (11) and associates, respectively. Fistulas were present in 20 of our 301 cases, an over-all incidence of 6.6 per cent. They occurred for the most part as a complication of gastrojejunal ulcers after gastroenterostomy, 16 of our 20 cases being in this group.

Hemorrhage occurs more commonly in gastrojejunal ulcer than in duodenal ulcer, but it is rarely fatal since large vessels are not generally in the vicinity of the gastrojejunal anastomosis. Among our 301 patients 149 (about 50 per cent) gave a history or presented evidence of gastrointestinal hemorrhage at time of admission. The incidence of hemorrhage from gastrojejunal ulcer following gastroenterostomy was the same as that from ulcer following gastric resection.

DIAGNOSIS

The diagnosis of gastrojejunal ulcer may be difficult with the issue being settled only at the time of operation, or it may be made with relative ease. Whenever a patient who has undergone gastroenterostomy or gastric resection for peptic ulcer has symptoms of recurrence, gastrojejunal ulcer should be suspected. The gastric acidity of such a patient should be determined, and roentgenologic examination of the stomach after the ingestion of barium should be carried out. The concentration of gastric acids after a modified Ewald meal was determined for 268 of the 301 patients. Free hydrochloric acid was found in 78 per cent of the cases of gastrojejunal ulcer after gastric resection and in 96 per cent of those after gastroenterostomy. Roentgenologic examination of the stomach after ingestion of barium, although important, does not give entirely reliable results because of the difficulty of visualizing the ulcer. Roentgenologic findings in 275 of our cases indicated a lesion in 79 per cent of the cases of gastrojejunal ulcer after gastric resection and in 66 per cent of cases of ulcer after gastroenterostomy. However, a positive roentgenologic diagnosis of gastrojejunal ulcer was made in only 50 per cent of the cases of gastrojejunal ulcer after gastric resection and in 37 per cent of the cases after gastroenterostomy.

In 85 cases in which the size of the ulcer crater was given in the operative note, abnormalities had been noted on roentgenologic examination in 64 per cent of these cases, but a positive roentgenologic diagnosis of ulcer was made in only 36 per cent. From this it is evident that the roentgenologist has difficulty in demonstrating a gastrojejunal ulcer and that this difficulty is greater after gastroenterostomy than after gastric resection.

In cases in which roentgenologic demonstration of a gastrojejunal ulcer is not possible, gastroscopy may be of help. In 6 of our cases the gastroscopist made the diagnosis. A negative gastroscopic examination is not significant, as frequently the ulcer is situated in the jejunum distal to the stoma and beyond the view of the gastroscopist.

The roentgenologic diagnosis of gastrojejunocolic fistula is much easier than that of a gastrojejunal ulcer. In the present series, 16 of 20 patients had barium enemas and the fistula of each was demonstrated. Thir-

TABLE III.—DEATHS IN HOSPITAL AFTER OPERATIONS FOR GASTROJEJUNAL ULCER

Case No.	*Age, yrs., sex*	*Previous operation*	*Symptoms and signs*	*Operation*	*Cause of death*
			GASTROJEJUNAL ULCER AFTER GASTRIC RESECTION		
1	37M	⅔ stomach removed (elsewhere)	Pain; many gastrointestinal hemorrhages; hypertension (200/120)	Transthoracic vagotomy	Cerebrovascular accident 39 days after operation
2	45M	Small part of stomach resected (elsewhere)	Pain; many gastrointestinal hemorrhages	Vagotomy and gastric re-resection	Volvulus of jejunum 14 days after operation; resection, oliguria and uremia
3	52M	Small part of stomach resected (elsewhere)	Pain; many gastrointestinal hemorrhages	Vagotomy and gastric re-resection	Acute pancreatitis 17 days after operation
4	57M	½ stomach removed (elsewhere)	Pain; many gastrointestinal hemorrhages; active syphilis	Gastric re-resection	Duodenal fistula; subhepatic abscess; gastrointestinal hemorrhage 54 days after operation
5	59M	½ stomach removed (elsewhere)	Pain; diarrhea, loss of weight, and acute perforation of gastroileal ulcer	Gastric re-resection	Cerebral hemorrhage 17 days after operation
			GASTROJEJUNAL ULCER AFTER GASTROENTEROSTOMY		
6	60M	Gastroenterostomy (elsewhere)	Pain; 1 gastrointestinal hemorrhage	Gastric resection	Duodenal fistula, subphrenic and subhepatic abscess 18 days after operation

teen patients had roentgenologic examination of the stomach with barium and the fistula of only 1 was demonstrated, although 11 had positive findings of a gastrojejunal ulcer.

TREATMENT AND OPERATIVE MORTALITY

When the diagnosis of gastrojejunal ulcer has been made, surgical intervention should be advised unless contraindicated by the patient's poor general condition. When surgical treatment is contraindicated, which it seldom is, a medical regimen of the same type as that used in the treatment of a duodenal ulcer should be employed with the anticipation that the patient's condition will improve so that operation will be possible when it does.

Modern surgical treatment of gastrojejunal ulcer resolves itself into vagotomy alone or combined with other procedures, and adequate gastric resection with removal of approximately two-thirds of the stomach. There are definite indications for both of these procedures. Since the surgical management of a gastrojejunal ulcer following gastric resection differs from that following gastroenterostomy, the treatment used in each series of cases will be presented separately. The treatment of the cases of gastrojejunocolic fistula will be considered later.

Gastrojejunal ulcer after gastric resection. In 88 of the 115 cases of gastrojejunal ulcer after gastric resection vagotomy was performed with 1 death, an operative mortality of 1.1 per cent. Fourteen patients underwent vagotomy and gastric resection, with 2 deaths, an operative mortality of 14.3 per cent. The remaining 13 patients had gastric re-resection, with 2 operative deaths, a mortality of 15.3 per cent. Thus in this group of 115 cases of gastrojejunal ulcer after gastric resection there were 5 deaths, an operative mortality of 4.3 per cent.

The postoperative deaths are summarized in Table III.

Gastrojejunal ulcer after gastroenterostomy. Among the 186 patients with gastrojejunal ulcer after a gastroenterostomy 1 (0.5 per cent) died after operation. Of these patients 145 were treated by taking down the gastroenteric anastomosis and partial gastric resection with 1 operative death, a mortality rate of 0.7 per cent; 29 were treated by vagotomy alone, 3 by vagotomy and gastric resection, and 9 by vagotomy and other operations. There were no deaths among the patients treated by vagotomy. Included among the patients treated by vagotomy and other operations were 3 on whom the gastroenteric anastomosis was taken down and pyloroplasty was carried out, 2 on

TABLE IV.—GASTRIC ACIDITY BEFORE AND AFTER OPERATION FOR GASTROJEJUNAL ULCER

Previous operation and time of test in relation to operation for gastrojejunal ulcer	*Acids determined, cases*	*Achlorhydria*		*Free hydrochloric acid*	
		No. of cases	*Per cent*	*No. of cases*	*Per cent*
VAGOTOMY GROUP					
Previous gastroenterostomy					
Preoperative	34	0	—	34	—
Postoperative	25	7	28.0	18	72.0
Previous gastric resection					
Preoperative	95	21	22.1	74	77.9
Postoperative	55	42	76.4	13	23.6
GASTRIC RESECTION GROUP					
Previous gastroenterostomy					
Preoperative	127	7	5.5	120	94.5
Postoperative	21	18	85.7	3	14.3
Previous gastric resection					
Preoperative	12	3	25.0	9	75.0
Postoperative	4	3	75.0	1	25.0
TOTAL GROUP					
Previous gastroenterostomy					
Preoperative	161	7	4.3	154	95.7
Previous gastric resection					
Preoperative	107	24	22.4	83	77.6

whom the gastroenteric anastomosis was taken down, and 4 who had excision of gastrojejunocolic fistula.

RESULTS

In our series, 242 patients were followed 1 to 8 years and the results were classified as follows: (1) excellent, when the patient had no symptoms of ulcer and no evidence of disturbance of motility, such as gastric retention, diarrhea, or bloating; (2) unsatisfactory when symptoms were suggestive of recurrent ulceration but such ulceration is not proved, or when symptoms of motility disturbance are present; and (3) poor when recurrent ulceration is proved either by roentgenologic examination, at operation, or both.[1] The follow-up was by examination and laboratory studies, and questionnaire.

Cases of gastrojejunal ulcer after gastric resection. We were able to follow 94 of the 115 patients in this group. Of these, 78 were treated by vagotomy alone with excellent results in 70.5 per cent, unsatisfactory results in 11.5 and poor results in 18.0 per cent. Nine patients had vagotomy combined with a gastric re-resection; all had excellent results. Of the 7 traced patients who had gastric re-resection alone, only 57.1 per cent had excellent results.

In cases of gastrojejunal ulcer after gastroenterostomy. Of the 186 patients in this group 148 were traced. Twenty-seven of these were treated by vagotomy alone with excellent results in 77.8 per cent, unsatisfactory results in 11.1 per cent, and poor results in 11.1 per cent. Two patients had vagotomy and gastric resection; 1 had an excellent result and 1 an unsatisfactory result. Of the 8 followed who had vagotomy and other operations, 50 per cent obtained excellent results, 25 per cent unsatisfactory, and 25 per cent poor results.

Of the 111 patients followed after their gastric resection, 86.5 per cent had excellent results, 4.5 per cent unsatisfactory results, and 9.0 per cent poor results.

Relief of hemorrhage. Of the 124 patients in the vagotomy group followed, 13 had further hemorrhage while 111 (89.6 per cent) had no further hemorrhage.

Of the 118 patients followed who had gastric resection or re-resection, only 4 had further hemorrhages while 114 (96.6 per cent) did not.

Postoperative acidity as indicated by the insulin test. The Hollander insulin test was performed on 71 patients after vagotomy with

[1]This is the same classification that one of us (10, 12) has used in all previous studies reported on vagotomy.

negative tests in 61[1] and positive in 10. As Walters, Priestley, and Belding have shown previously, there was uncertain correlation between the results of this test and the final results. Of the 54 patients followed who had negative insulin tests, 69 per cent had excellent results yet 5 of the 9 followed who had positive insulin tests also had excellent results.

Gastric acidity before and after vagotomy and gastric resection. In the vagotomy group the concentration of gastric acid was determined preoperatively for 34 patients who had previous gastroenterostomy and all 34 had free hydrochloric acid with a mean value of 33.5 degrees (Töpfer's method). Values for acids were determined after operation on 25 of these patients. Seven were achlorhydric and 18 still had free acid with a mean value of 27.9 degrees.

Of the 95 patients in the vagotomy group with gastrojejunal ulcer following resection on whom acids were determined preoperatively, 21 were achlorhydric while 74 had free acids with a mean value of 27.5 degrees. Of these, 55 had acids determined postoperatively; 42 were achlorhydric while 13 had free hydrochloric acid with a mean value of 25.5 degrees (Table IV).

In the resection group preoperative acidity was determined on 127 patients with gastrojejunal ulcer after gastroenterostomy, 7 of whom were achlorhydric, while 120 had free hydrochloric acid with a mean value of 36.4 degrees. Postoperatively 21 of these patients had their acids determined; 18 were achlorhydric while 3 had free hydrochloric acid with a mean value of 15.3 degrees. Of those having gastrojejunal ulcer after previous resection 12 had acids evaluated preoperatively; 3 were achlorhydric and 9 had free hydrochloric acid with a mean value of 36.6 degrees. Four of these patients had acids determined postoperatively; 3 were achlorhydric and 1 had free acids.

Vagotomy by transthoracic and transabdominal approaches. Of the patients in the vagotomy group 117 had vagotomy alone; 67 of these operations were done by the transthoracic route and 50 by the transabdominal. Of the 63 patients followed after transthoracic vagotomy 71 per cent had an excellent result while of the 42 followed after transabdominal vagotomy 74 per cent had an excellent result.

[1]The "negative Hollander test" was originally thought to indicate complete vagotomy.

TABLE V.—RESULTS OF SURGICAL TREATMENT IN 20 CASES OF GASTROJEJUNOCOLIC FISTULA

Surgical treatment	*No. operated on*	*No. followed*	*Results*		
			Excellent	*Unsatisfactory*	*Poor*
		PREVIOUS OPERATION: GASTROENTEROSTOMY			
Fistula excised, openings in colon and jejunum closed plus:					
Partial gastric resection	12	8	7	—	1
Vagotomy	4	4	3	1	—
		PREVIOUS OPERATION: GASTRIC RESECTION			
Vagotomy and gastric re-resection	3	2	2	—	—
Gastric re-resection	1	1	1	—	—

Gastrojejunocolic fistula. Results of treatment of 20 patients with gastrojejunocolic fistula were good (Table V). Sixteen of the fistulas followed gastroenterostomy and 4 gastric resection. There were no operative deaths.

Twelve fistulas that developed after gastroenterostomy were treated by excision of the fistulas with closure of the openings in the colon and jejunum and partial gastric resection. Eight of these patients were followed; 7 had excellent results and 1 a poor result. The remaining 4 patients whose fistulas followed gastroenterostomy had the fistulas excised, openings in the colon and jejunum closed, and vagotomy. We were able to follow all 4 of these patients. Three had excellent results and 1 an unsatisfactory result. The patient with fistula who had a poor result was found to have a recurrent gastrojejunal ulcer which responded well to medical management, while the patient whose result was classified as unsatisfactory had been troubled by diarrhea since vagotomy and was suspected of having further ulceration because of a gastrointestinal hemorrhage.

Of the 4 patients whose gastrojejunocolic fistulas followed previous gastric resection, 3 were treated by excision of the fistula with closure of the colon and jejunal openings, gastric re-resection, and vagotomy. Results are shown in Table V.

We were able to follow 15 of the 20 patients who had gastrojejunocolic fistulas; 6.7 per cent had a poor result, 6.7 per cent an unsatisfactory result, while 86.6 per cent had an excellent result. None had a recurrence of their fistulas, and there were no operative deaths.

COMMENT

To evaluate the effectiveness of any surgical procedure for gastrojejunal ulcer sufficient time must elapse. Many studies have shown that the interval between the previous gastric resection and the appearance of a gastrojejunal ulcer is shorter than that between gastroenterostomy and the appearance of gastrojejunal ulcers. In our cases we have not attempted to determine the time interval between operation for duodenal ulcer and the onset of symptoms suggesting recurring ulceration. We have studied the time interval between the original operation and the re-operation for recurrence. The interval between the gastroenterostomy and the operation for gastrojejunal ulcer in this study was 11.2 years and between gastric resection and operation for recurrence was 3.7 years.

Vagotomy is generally accepted as the treatment of choice for gastrojejunal ulcer following resection of at least two-thirds of the stomach. The present study indicates that vagotomy can be expected to give excellent results in 70 per cent of such cases and carries a low operative risk. Whether vagotomy is done by the transthoracic or transabdominal route makes little difference as far as the ultimate result is concerned, but the objections to the transthoracic approach are that the surgeon is denied the opportunity of examining the gastrojejunal anastomosis to determine the true status of the ulceration or inflammation (for sometimes an ulcer is not present) and the exact amount of stomach remaining. Many of these patients have considerable postoperative thoracic pain which may last for many weeks and be most distressing.

Gastric resection gives superior results to vagotomy in cases of gastrojejunal ulcer after gastroenterostomy. In our series gastric resection yielded excellent results in 86.5 per cent of 111 traced cases of this type as compared to 77.8 per cent from vagotomy alone.

Our findings indicate that in more than 70 per cent of the cases in which the gastrojejunal ulcer develops after an inadequate resection of a third to a half of the stomach, vagotomy can be expected to give excellent results with a low operative mortality, whereas re-resection in this series carries a prohibitively high operative mortality. However, if re-resection is deemed advisable by the surgeon, then vagotomy may be added without greatly increasing the operative risk, and may give the patient additional protection against further ulceration.

It is significant that in the vagotomy group free hydrochloric acid was present before vagotomy in all cases in which gastrojejunal ulcers developed after gastroenterostomy, but it was present in only 77.9 per cent of cases in which the ulcers developed after gastric resection. Vagotomy produced achlorhydria in only 28 per cent of cases in which the ulcers had followed gastroenterostomy, and in 54 per cent of the cases in which the ulcer had followed gastric resection.[1] It is likewise significant that in the resection group free hydrochloric acid was present before resection in about 95 per cent of cases in which gastrojejunal ulcers developed after gastroenterostomy and in 75 per cent of cases in which ulcers developed after gastric resection. Gastric resection produced achlorhydria in 80[2] per cent of the cases in which the ulcers had followed gastroenterostomy. Gastric re-resection pro-

[1]This figure may be arrived at from Table IV by subtracting the percentage of cases of achlorhydria before vagotomy from those after vagotomy.

[2]This figure may be arrived at from Table IV by subtracting the percentage of cases of achlorhydria before resection from those after gastric resection.

duced achlorhydria in 50 per cent of the cases in which the ulcer had followed gastric resection. The greater incidence of achlorhydria undoubtedly accounts to a large extent for the better results after gastric resection than after vagotomy following gastroenterostomy.

Recognition of a gastrojejunal ulcer by roentgenologic examination may be most difficult. The roentgenologist can detect a gastrojejunal ulcer after a previous gastric resection more easily than after previous gastroenterostomy, but there is a high incidence of error in both. Therefore, a patient who has undergone gastroenterostomy or gastric resection for duodenal ulcer and who shows recurrent symptoms, should be suspected of having a gastrojejunal ulcer. If, in addition to these symptoms, the patient has had hemorrhage from the upper part of the gastrointestinal tract, a presumptive diagnosis of jejunal ulcer can be made and in most cases operation should be carried out.

Gastrojejunal ulcers like duodenal ulcers tend to heal and to recur. Since operation is rarely necessary as an emergency procedure for gastrojejunal ulcers, the findings at the gastrojejunal anastomosis may not be pronounced—that is, ulcer with a crater. However, in such an individual the finding of inflammation in the region of the gastrojejunal anastomosis or of a scar indicating a previously healed ulcer should be sufficient evidence of a gastrojejunal ulcer for the surgeon to carry out a definitive procedure for treatment of a gastrojejunal ulcer.

The surgical treatment of gastrojejunocolic fistula in the past has carried a high operative mortality whereas in this series of 20 cases there were no operative deaths. This reflects not only improved surgical techniques, but demonstrates the important role of antibiotics, improved anesthesia, and better supportive measures which are available today.

SUMMARY

Between the years 1945 and 1952, inclusive, 617 operations were performed on 586 patients for gastrojejunal ulcer. Included in this study are 301 of these patients, 143 having undergone vagotomy alone or combined with additional procedures, and 158 having undergone either gastric resection or a reresection, in the treatment of gastrojejunal ulcer.

Gastrojejunal ulcers following gastroenterostomy differ from those following gastric resection both in certain clinical features and their surgical management. Gastrojejunal ulcers developed after gastric resection in 115 patients and after a previous gastroenterostomy on 186 included in this study. The interval between the previous and definitive operation for gastrojejunal ulcer was 3.7 years for those having previous gastric resection and 11.2 years for those having previous gastroenterostomy. Of the gastrojejunal ulcers developing after an operation 96.3 per cent occurred in cases of duodenal ulcer, 2.0 per cent in cases of gastric ulcer, and 1.7 per cent in cases of gastric and duodenal ulcer. Ninety-one per cent occurred in men and 9 per cent in women. Seventy-eight of the 301 patients had undergone multiple previous operations for peptic ulcer. Six and six-tenths per cent of the patients had gastrojejunocolic fistulas, the majority occurring after a gastroenterostomy. Hemorrhage occurred in about 50 per cent of the patients in the series.

Preoperative gastric analysis revealed free hydrochloric acid in 78 per cent of the patients with gastrojejunal ulcers after previous gastric resection and in 96 per cent of those with gastrojejunal ulcers after previous gastroenterostomy. A positive roentgenologic diagnosis of gastrojejunal ulcer was made in 50 per cent of the cases in which the ulcer followed gastric resection and in 37 per cent of those in which the ulcer followed gastroenterostomy. A gastrojejunocolic fistula can be demonstrated in 100 per cent of the cases by barium enema.

Of the 115 patients with gastrojejunal ulcers after previous gastric resection 88 were treated by vagotomy with a mortality of 1.1 per cent, 14 by vagotomy and gastric re-

resection with a mortality of 14.3 per cent and 13 by gastric re-resection with a mortality of 15.3 per cent. Of the 186 patients with gastrojejunal ulcers after gastroenterostomy 29 were treated by vagotomy alone, 3 by vagotomy and gastric resection, 9 by vagotomy combined with other operations, and 145 by the taking down of the gastroenteric anastomosis, excision of the ulcer, and partial gastric resection. There were no deaths after any of the vagotomy procedures and only 1 death after the 145 resections, a mortality of 0.7 per cent.

Two hundred forty-two of the patients were followed 1 to 8 years, either by return visit or questionnaire. Gastrojejunal ulcers developing after gastric resection are best treated by vagotomy alone or combined with another procedure. Vagotomy alone gave excellent results in 70.5 per cent of the 78 patients so treated. Vagotomy and gastric re-resection in 9 cases gave excellent results in all cases, while gastric re-resection alone gave excellent results in only 57.1 per cent of 7 traced cases in which it was employed.

A gastrojejunal ulcer which follows previous gastroenterostomy is best treated by a taking down of the anastomosis, excision of the ulcer, and adequate gastric resection. This procedure gave excellent results in 86.5 per cent of all traced patients with ulcers of this type who were so treated, and 77.8 per cent of 27 patients with such ulcers had excellent results following vagotomy.

Gastrointestinal hemorrhage recurred after vagotomy for gastrojejunal ulcer in 10.4 per cent of cases whereas hemorrhage recurred in only 3.4 per cent after a gastric resection or re-resection.

After operation 71 patients undergoing vagotomy had insulin tests. The tests were negative in 86 per cent. Gastric analysis after vagotomy disclosed that 28 per cent of the patients with gastrojejunal ulcers after a previous gastroenterostomy and 54 per cent of those who had previous gastric resection were rendered achlorhydric by the operation. Similarly of those treated by gastric resection or re-resection, 81 per cent of those with gastrojejunal ulcers after previous gastroenterostomy and 50 per cent of those with ulcers after previous gastric resection were rendered achlorhydric by the operation.

The end results from vagotomy performed by the transabdominal or transthoracic routes showed no significant difference.

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THE AGE FACTOR IN THE MORTALITY RATE OF PATIENTS UNDERGOING SURGERY OF THE BILIARY TRACT

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THERE HAS BEEN a gradual increase in the proportion of older individuals who have been accepted for surgical treatment of biliary tract disease, both benign and malignant, during the past 20 years. The actual number of such patients has become much greater for the country as a whole, not only because of the growth of the total population but also because of the apparent increased incidence of cholelithiasis among our people and their ever-increasing age span. In a study of the causes of death occurring after biliary tract surgery it was, of course, apparent that the mortality rate was higher in the older age group. It has also been evident that each year the proportion of patients in this aged group who present themselves for surgical treatment in this center is increased. For example, in 1933 there were 176 patients operated upon for nonmalignant disease of the biliary tract, of this number there were 42 over 50 years of age. In 1952, 106 of the total of 181 patients operated upon for nonmalignant disease of the biliary tract were over 50 years of age. These are not unusual years, but represent the trend of the last two decades, in this center. Carp, Cutler, Bosch, Welch, and others have described at length the increasing importance of gerontology in modern medicine.

The aged patient with biliary tract disease presents unique diagnostic and therapeutic problems. Parallel with the rise in mean age of the general population and the growth of large public institutions devoted exclusively to the care and study of the aged has been the recognition that biliary tract disease represents the most frequent single incident for abdominal surgical intervention in geriatric patients, as Strohl and Diffenbaugh have pointed out.

The present study consists of an analysis of the cases of biliary tract disease in aged patients seen in this center[1] since 1932. In contradistinction to the reports from solely geriatric hospitals, i.e., Carp, Cutler, Rosenthal, we are able to compare these data with those from the larger group of younger patients with biliary tract disease treated at the same time and under the same general conditions.

THE NEW YORK HOSPITAL SERIES

During the 21 year period (September 1, 1932 to September 1, 1953) 328 cases of benign biliary tract disease in patients 65 years of age or over were treated by surgery in this clinic. During the same period, 1,355 patients 50 to 64 years of age, and 2,287 patients under 50 years of age were treated for similar conditions. Among this same age group (patients 65 years of age or older) during an identical period, 29 cases of carcinoma of the gallbladder and 5 cases of carcinoma of the extrahepatic ducts[2] were diagnosed at laparotomy or at autopsy (Table I).

Diagnostic Classification

Two hundred and twenty-five of these geriatric patients were treated for chronic cholecystitis, 92 for acute cholecystitis, and 11 for postoperative and other benign strictures of the choledochus (Table I). The percentage of patients with acute cholecystitis as opposed to chronic biliary tract disease in the total series was 19.2 per cent among

From the Department of Surgery, The New York Hospital—Cornell Medical Center, New York.

[1]The New York Hospital—Cornell Medical Center (pavilion cases).

[2]Not including ampullary carcinomas.

TABLE I.—DIAGNOSTIC CLASSIFICATION OF 362 PATIENTS (65 YEARS AND OVER) WITH BILIARY TRACT DISEASE*

	No. of cases
Chronic cholecystitis	225
Acute cholecystitis	92
Postoperative strictures and miscellaneous benign conditions	11
Total benign conditions	328
Carcinoma of the gallbladder	29
Carcinoma of the extrahepatic biliary ducts	5†
Total malignant conditions	34
Total	362

*Confirmed by operation and/or autopsy.
†Not including the ampulla of Vater.

those under 50 years of age, 21.3 per cent among those 50 to 64 years of age, and 29.2 per cent among those 65 years of age and older (Table II).

Operative Procedures Employed

The operative procedures employed in the treatment of these geriatric patients are shown in Table III. Simple cholecystectomies were performed in 47 cases of acute cholecystitis (mortality 6.4 per cent) and in 132 cases of chronic cholecystitis (mortality 3 per cent). Cholecystostomy was employed in 32 acute cases (mortality 15.6 per cent) and in 11 chronic cases (mortality 27.2 per cent).

Exploration of the choledochus with cholecystectomy was performed in 13 cases of acute disease (mortality 15.3 per cent) and 59 cases of chronic cholecystitis (mortality 3.4 per cent). Simple choledochotomy was carried out in 23 patients in the chronic group with 1 fatality (mortality 4.3 per cent).

Comparative Mortality

Thirteen hundred and fifty-five patients 50 to 64 years of age are used here as a control group. These individuals were subjected to surgery for benign biliary tract disease during the same period under similar conditions. A comparison of the mortality in these patients, subjected to the same series of operative procedures for acute and chronic cholecystitis, with the geriatric group is found in Tables IV and V.

TABLE II.—INCREASED INCIDENCE OF ACUTE CHOLECYSTITIS IN AGED PATIENTS (1,645 PATIENTS 50 YEARS OF AGE AND OVER*)

Age group	*Acute*		*Chronic*		*Total*
	No.	*Per cent*	*No.*	*Per cent*	
50–64 yrs. old	283	21.3	1045	78.6	1328
65 yrs. and over	92	29.2	225	70.9	317

*38 patients (27, 50–64 years and 11, 65 years and over) with a diagnosis of stricture were excluded from this table.

The mortality among patients with acute cholecystitis (including those with choledochal calculi) over 65 years of age was 10.9 per cent. For similar cases in the control age group (50 to 64 years) the mortality was 2.1 per cent (Table IV). This was further divided in respect to the operative procedure employed. When simple cholecystectomy was performed in such acute cases the mortality for the geriatric group was 6.4 per cent while the mortality following simple cholecystectomy in the control group was 0.9 per cent. In the geriatric group the mortality following cholecystostomy was 15.6 per cent and following cholecystectomy plus choledochotomy it was 15.4 per cent (all with acute cholecystitis). Corresponding procedures employed on patients in the younger age group (50 to 64 years) were accompanied by mortalities of 6.9 per cent and 7.4 per cent respectively (all with acute cholecystitis).

The mortality among patients with chronic cholecystitis (including those with choledochal calculi) who were over 65 years of age was 4.4 per cent (Table V). In the corresponding group of patients, between the ages of 50 to 64 years, the mortality was 2.6 per cent. A similar division of this group in respect to the mortality following each type of operative procedure employed was made. Following simple cholecystectomy the mortality for patients over 65 years of age was 3 per cent; while in the age group 50 to 64 years for the same procedure the mortality was 1.4 per cent (all with chronic cholecystitis). Following simple choledochotomy, the mortality was identical (4.3 per cent) for the two groups. When cholecystectomy was combined with choledochotomy the mortality for patients over 65 years of age was 3.4 per cent, while for those 50 to 64 years it was 6.9 per cent.

Causes of Death

The causes of death following surgery for benign biliary tract disease in this center are outlined in Table VI. There were 15 fatalities (mortality 0.6 per cent) among 2,287 operative cases in patients less than 50 years of age; 34 fatalities (mortality 2.5 per cent) among 1,355 operative cases in which the patient's age was 50 to 64 years; and 22 fatalities (mortality 6.7 per cent) among 328 operative cases in patients 65 years of age and older. The range of causes of death among these patients of diverse ages is remarkably similar (Table VI).

In the group of patients 65 years of age and over, there were 130 cases of hypertensive cardiovascular disease (for criterion see next section) with a mortality of 6.1 per cent; 52 cases of arteriosclerotic heart disease (mortality 7.6 per cent); 19 cases of severe, chronic pulmonary disease (mortality 10.5 per cent); and 6 cases of nonbiliary cirrhosis (mortality 33.3 per cent) (Table VIII and section on "Preoperative Evaluation").

The most frequent cause of death was common to all age groups, namely, hepatic insufficiency secondary to cirrhosis and infection—the patients with long standing biliary tract disease requiring multiple operative procedures.

Among the patients 65 years of age and over, acute coronary occlusion was the second principal cause of death. Fatal pulmonary infarction was more frequently encountered among the less aged patients (50 to 64 years).

Nonfatal Complications

There were 32 nonfatal complications among the geriatric group, 14 occurring in patients with acute cholecystitis and 18 among those with chronic cholecystitis (Table VII). In comparison there were 98 complications in the control group (age 50 to 64 years) a group which was 4.1 times as large. Twenty-six of these were found in cases of acute cholecystitis and 72 among cases of chronic cholecystitis. Wound infection was the most frequently encountered nonfatal complication among the geriatric patients; while this condition and bronchopneumonia were approximately equally prevalent as complications in the control group (ages 50 to 64 years).

TABLE III.—MORTALITY FOLLOWING OPERATIVE PROCEDURES IN PATIENTS 65 YEARS OF AGE AND OVER

	No. of cases	*Deaths**	*Mortality rate, per cent*
Acute cholecystitis—92 patients			
Cholecystectomy	47	3	6.37
Cholecystostomy	32	5	15.6
Cholecystectomy plus choledochotomy	13	2	15.3
Total	92	10	10.08
Chronic cholecystitis—225 patients			
Cholecystectomy	132	4	3.03
Cholecystostomy	11	3	27.2
Cholecystectomy plus choledochotomy	59	2	3.38
Choledochotomy	23	1	4.3
Total	225	10	4.4

*Including all deaths during the hospitalization in which the operative procedure was performed.

The incidence of nonfatal complications following biliary tract procedures for chronic cholecystitis was almost identical (8 per cent and 7 per cent) in the aged and younger groups. Following procedures for acute cholecystitis, in contrast, the complication rate among the geriatric group was 15 per cent; while among the younger age group it was 9 per cent. Wound infection, separation, hematoma formation, and evisceration —evidence of poor wound healing—were not significantly different in the two age groups. The incidence of phlebitis and bronchopneumonia (although not pulmonary infarcts) was higher in the younger patients. Cerebrovascular accidents and coronary occlusion formed a slightly higher percentage of nonfatal complications among the aged group.

Preoperative Evaluation

For the purpose of attempting to predict the occurrence of postoperative fatalities and complications, the 328 operative cases were classified according to the major degenerative disease processes[1] discernible in

[1]This classification was not altered as postoperative complications developed.

TABLE IV.—THE MORTALITY FOLLOWING OPERATIVE PROCEDURES FOR THE TREATMENT OF ACUTE CHOLECYSTITIS IN THE AGED (375 PATIENTS 50 YEARS OF AGE AND OVER)

Procedures	*50 to 64 yrs. of age*			*65 yrs. of age and over*		
	Cases	*Deaths*	*Mortality, per cent*	*Cases*	*Deaths*	*Mortality, per cent*
Cholecystectomy	227	2	0.88	47	3	6.37
Cholecystostomy	29	2	6.89	32	5	15.62
Cholecystectomy plus choledochotomy	27	2	7.4	13	2	15.38
Totals	283	6	2.12	92	10	10.86

their preoperative state (Table VIII). The mortality for the entire group was 6.7 per cent (22 postoperative deaths). The preoperative classification included:

1. One hundred and twenty-four patients (not the largest group) were regarded as having no major degenerative disease process. These patients did have generalized arteriosclerosis, osteoarthritis, diverticulosis, benign prostatic hypertrophy.[1] They did not have the disease processes listed to a major degree. There were 19 nonfatal complications (14.4 per cent) and 4 fatalities (3.2 per cent) among the aged patients in this group without recognized major disease processes.

2. Hypertensive cardiovascular disease was present in 130 patients (the largest group). These were patients with a sustained systolic blood pressure over 160 or diastolic blood pressure over 90. They had enlarged hearts with left ventricular preponderance. The highest consistent pressure was 200/145 and the average 210/100–120. There were no cases of malignant hypertension. There were 20 complications (15.3 per cent) and 8 deaths (6.1 per cent) following surgery in this group.

3. Arteriosclerotic heart disease of a significant degree was noted in 52 patients. These individuals had sustained previous coronary occlusion (by electrocardiographic study) or had demonstrated electrocardiographic changes of a less marked degree associated with angina pectoris or cardiac decompensation. There were 11 complications (21.2 per cent) and 4 deaths (7.6 per cent) in this group following surgical intervention for biliary tract disease.

4. Severe, chronic primary pulmonary disease was present in 19 cases, consisting of severe emphysema and bronchiectasis. There were 2 nonfatal complications (10.5 per cent) and 2 fatalities following surgery among these patients.

5. Diabetes mellitus of a degree requiring a significant daily insulin administration was present in 17 cases. There were 2 nonfatal complications and no postoperative deaths in this group.

6. Cirrhosis, complicated by either hemorrhage from esophageal varices, ascites, or jaundice, was present in 6 instances (by preoperative evaluation). There were 2 postoperative deaths in this group (33.3 per cent) following biliary tract surgery.

[1]In 7 cases prostatectomy was performed prior to cholecystectomy.

TABLE V.—THE MORTALITY FOLLOWING OPERATIVE PROCEDURES FOR THE TREATMENT OF CHRONIC CHOLECYSTITIS IN THE AGED (1,270 PATIENTS 50 YEARS OF AGE AND OVER)

Procedures	*50 to 64 yrs. of age*			*65 yrs. of age and over*		
	Cases	*Deaths*	*Mortality, per cent*	*Cases*	*Deaths*	*Mortality, per cent*
Cholecystectomy	842	12	1.4	132	4	3.03
Cholecystostomy	8	1	12.5	11	3	27.3
Choledochotomy	47	2	4.3	23	1	4.3
Cholecystectomy plus choledochotomy	143	10	6.9	59	2	3.4
Cholecystostomy plus choledochotomy	5	3	60.0	—	—	—
Totals	1045	28	2.6	225	10	4.4

Preoperative Evaluation in Elective Cases

A group of greater interest are those aged patients (65 years of age and over) in whom the decision to perform biliary tract surgery was entirely an elective one. Patients with a clinical (preoperative) diagnosis of choledochal calculus or acute cholecystitis, i.e., those requiring emergency or urgent procedures, were not included in this group. These patients, in contrast, entered the hospital for a complete evaluation of their biliary tract disease as well as the additional conditions prevalent among aged patients. Following a thorough study of these disease

processes, they were prepared for and subjected to an elective cholecystectomy with or without choledochotomy as decided upon at the operating table.

In this group (166 patients), from which the emergency cases had been removed, the incidence and relative frequency of occurrence of the major degenerative disease processes are similar to those in the entire aged group (Tables VIII and IX). The complication rate was 11.4 per cent and the mortality 1.8 per cent. Fifty-six of these patients fell into that category in which no major degenerative disease process was discernible. There were 7 nonfatal complications (12.5 per cent) and no deaths in this group. Hypertensive cardiovascular disease was noted (as previously defined) in 65 patients. In this group there were 8 complications (12.9 per cent) and 1 death (1.5 per cent). Among the patients with significant arteriosclerotic heart disease there was 1 fatality; and in the group with chronic pulmonary disease an additional postoperative death (Table IX). There were no deaths, and but 2 complications in those groups with severe diabetes and miscellaneous disease processes. It should be noted that these patients exhibited the presence of the less severe disease processes, i.e., generalized arteriosclerosis, benign prostatic hypertrophy, osteoarthritis, and diverticulosis, to the same degree as the total group; and that the incidence of the major degenerative disease processes among them was similar to that in the total group. The significant difference between these two groups (Table VIII and IX) was solely the presence or absence of an acute process in the biliary tract.

TABLE VI.—FATALITIES FOLLOWING SURGERY FOR NONMALIGNANT DISEASE OF THE BILIARY TRACT

*Cause of death**	*2,287 patients under 50 yrs.*	*1,355 patients 50–64 yrs.*	*328 patients 65 yrs. and over*	*Totals*
Hepatic insufficiency (cirrhosis, infection, necrosis)	4	9	7	20
Acute pulmonary disease (pulmonary emboli)	3 (2)**	8 (5)	2 (1)	13 (8)
Peritonitis	1	3	2	6
Intraperitoneal abscess and/or fistula	1	4	0	5
Pancreatitis, acute	2	0	1	3
Renal insufficiency	2	0	2	4
Coronary occlusion, acute.	0	2	4	6
Cardiac failure (no acute coronary occlusion)	0	2	0	2
Miscellaneous	2	6	4	12
Total mortality	15 (0.6%)	34 (2.5%)	22 (6.7%)	71 (1.8%)

*70 per cent confirmed by autopsy.
**Pulmonary emboli.

DISCUSSION

The Unique Aspects of Biliary Tract Disease in Aged Patients

The apparent increased incidence of acute cholecystitis. The conclusion that acute cholecystitis is more prevalent with advancing age is reached or suggested in every large series of geriatric biliary tract cases, i.e., Strohl and Diffenbaugh and Welch. It might be attacked, however, on the grounds of physician selection prior to arrival at the hospital, i.e., referring doctors send all cases of apparent acute cholecystitis to the hospital while among patients with symptoms referable to chronic cholecystitis the older patients may be retained for care at home. Furthermore, the older patients themselves may be less inclined to seek hospital care

TABLE VII.—NONFATAL COMPLICATOINS FOLLOWING BILIARY TRACT SURGERY IN GERIATRIC PATIENTS

Nonfatal complications	*Patients 50 to 64 yrs. 1,355 cases*		*Patients 65 yrs. and over 328 cases*	
	Acute (283)	Chronic (1,052)	Acute (92)	Chronic (236)
Coronary occlusion	0	3	0	1
Auricular fibrillation (new)	1	2	2	0
Cerebrovascular accidents	0	0	0	2
Mental confusion (etiology unknown)	1	0	0	0
Pulmonary infarction	3	3	1	2
Phlebitis (without pulmonary infarction)	1	11	1	0
Bronchopneumonia, pleurisy	4	17	0	2
Atelectasis, pulmonary	5	6	2	0
Wound infection	5	17	4	4
Wound separation, hematoma, evisceration	1	2	2	0
Persistent biliary fistula	2	4	2	1
Peritonitis, intra-abdominal abscess, septicemia	3	2	0	1
Pancreatitis, acute	0	0	0	2
Miscellaneous	0	5	0	3
Totals	26	72	14	18

TABLE VIII.—PREOPERATIVE EVALUATION OF 328 PATIENTS (65 YEARS OF AGE AND OLDER) IN RESPECT TO THE PRESENCE OF DEGENERATIVE DISEASE PROCESSES

	No. of patients*	Nonfatal complications		Mortality	
		No.	Per cent	No.	Per cent
No major degenerative disease processes	124	19	14.4	4	3.2
Hypertensive cardiovascular disease	130	20	15.3	8	6.1
Arteriosclerotic heart disease	52	11	21.2	4	7.6
Diabetes mellitus (moderate to severe)	17	2	11.7	—	—
Chronic pulmonary disease	19	2	10.5	2	10.5
Cirrhosis	6	—	—	2	33.3
Chronic renal disease	5	1	20.0	1	20.0
Miscellaneous major chronic disease	12	2	16.6	2	16.6

*37 patients are classified in 2 groups.

except when under the stress of acute symptoms.

A series of 240 patients, who entered The New York Hospital with complaints unrelated to the biliary tract and in whom a diagnosis of cholecystitis was made during treatment for this other primary disease process, was studied. Among these patients the relative incidence of acute cholecystitis[1] was likewise increased approximately five fold among the aged. Among 63 patients under 50 years of age, there was 1 case of acute cholecystitis (1.6 per cent); among 107 patients 50 to 64 years of age, 2 had acute cholecystitis (1.9 per cent); while among 70 patients 65 years of age and older, 7 of those with biliary tract disease first recognized at unrelated hospital admission had acute cholecystitis (10.3 per cent).

[1]This does not include postoperative acute cholecystitis.

TABLE IX.—PREOPERATIVE EVALUATION OF 166 PATIENTS 65 YEARS AND OLDER UNDER CONSIDERATION FOR ELECTIVE CHOLECYSTECTOMY (EXTENT OF DEGENERATIVE DISEASE PROCESSES)

Classification	No. of patients*	Complications		Mortality	
		No.	Per cent	No.	Per cent
No major degenerative disease process	56	7	12.5	—	—
Hypertensive cardiovascular disease	65	8	12.9	1	1.5
Arteriosclerotic heart disease	18	1	5.5	1	5.5
Diabetes mellitus (moderate to severe)	10	1	10.0	—	—
Pulmonary emphysema, chronic	12	1	8.3	1	8.3
Miscellaneous disease processes	8	1	12.5	—	—

*3 patients are classified in 2 groups.

We believe that this group of patients entered the hospital with relatively asymptomatic chronic cholecystitis. In the setting of hospital treatment for an unrelated disease, some of them developed superimposed acute cholecystitis. The percentage of those manifesting this change during this relatively well controlled hospitalization period was strikingly higher among patients over 65 years of age.

Among 76 patients in whom a diagnosis of gallbladder disease was made—but who left the hospital against the advice of the staff before surgery—the same relationship was found. Acute cholecystitis became an increasingly prominent clinical diagnosis as age advanced.

Studies of biliary tract disease among patients in geriatric institutions are not helpful in this regard because of the lack of a comparative younger group under similar institutional conditions, but the very high incidence of acute cholecystitis (percentage) in such reports is indicative of the condition established by other studies.

The relatively high incidence of choledocholithiasis. Clinical icterus, or a history of jaundice, is more prevalent among patients with benign biliary tract disease as age advances. This might be attributed to an increased incidence of subclinical hepatic insufficiency in the geriatric group.

The results of choledochotomy in these patients refute this claim. Exploration of the choledochus in 95 patients, 65 years of age or over, yielded calculi in 72 cases (76 per cent); while in 222 patients between the ages of 50 and 64 years requiring common duct exploration, calculi were found in 120 (54 per cent). This is even more marked among postcholecystectomy patients explored at a later date for possible common duct stone. Among these cases (64), calculi were located in 85 per cent of those patients over 65 years of age, and in only 55 per cent of those between the ages of 50 and 64 years.

This may reflect the increased tendency for spontaneous passage of common duct calculi in younger individuals. Quigley, Welch, and others note the increased incidence of choledocholithiasis in the aged. We have observed, in common with others, that choledochal calculi in the aged are larger and more inclined to be multiple than in younger individuals.

The possible absence of characteristic signs and symptoms in acute disease. In common with other acute intra-abdominal conditions, acute cholecystitis may provoke a singularly unimpressive response in some aged individuals. This is true both subjectively and by routine objective criterion. In approximately 10 per cent of such geriatric patients, acute cholecystitis may be unaccompanied by striking elevation of the temperature, pulse rate, or a leucocytosis. The patient may have minimal discomfort. The presence of localized pain and tenderness and/or an expanding abdominal mass may be the sole diagnostic criteria.

An increased incidence of associated biliary tract neoplasia. A fourth aspect of biliary tract disease in the aged concerns the increasing likelihood of encountering a carcinoma. Approximately 85 per cent of cases of carcinoma of the gallbladder, in which the presenting complaint is not the presence of liver metastasis, are clinically indistinguishable from nonmalignant biliary tract disease. These patients are then operated upon as for uncomplicated chronic cholecystitis with cholelithiasis or choledocholithiasis. In our experience we found that if the patient is under 50 years of age the statistical probability of encountering a carcinoma is substantially less than 1 per cent; but this rate increased with advancing age so that among patients 65 to 74 years of age it is 8.9 per cent; and among patients 75 years of age and over it is 12.8 per cent (Table X).

TABLE X.—AGE FACTOR IN THE INCIDENCE OF MALIGNANCY ENCOUNTERED IN OPERATIONS FOR BILIARY TRACT DISEASE

	Under 50 yrs.	*50–64 yrs.*	*65–74 yrs.*	*Over 75 yrs.*
Total operative cases biliary tract disease	2292	1396	315	47
Carcinoma of gallbladder or extrahepatic ducts	5	41	28	6
Per cent malignancy among operative cases	0.2	3	8.9	12.8

The Difference in Therapy in Aged Patients with Biliary Tract Disease

The apparent difference in the therapeutic approach to geriatric patients with biliary tract disease is, of course, the tendency to defer or reject operative intervention. In this clinic a review of patients with biliary tract disease over a 21 year period disclosed that for one reason or another surgery was not embarked upon in 3 to 4 per cent of the patients under 50 years of age, in 7 to 8 per cent of those 50 to 64 years of age, and in approximately 20 per cent of those over 65 years of age. In the series of Fisher and White, over 50 per cent of the aged patients with biliary tract disease were treated without surgical intervention. This conservatism appears to be, at least, in part, unwarranted. The relatively benign course of these aged patients undergoing elective gallbladder and common duct surgery, even in the presence of recognized advanced degenerative disease processes, is noteworthy. A similar conclusion is reached by Cole.

The most striking conclusion to be drawn from an analysis of these patients is that the elective biliary tract procedure is tolerated remarkably well by the geriatric patient, in fact the difference in the complication rate and mortality rate between the aged (over 65 years) and the control (50 to 64 years) groups is insignificant. In contrast, the aged patient tolerates emergency biliary tract procedures, either for simple acute cholecystitis or for acute cholecystitis with choledocholithiasis, relatively poorly. Both mortality and complication rates are strikingly higher than in patients in younger age groups. This observation supports the concept that elective cholecystectomy in the aged patient with symptomatic biliary tract disease is even more important than in the younger patient, who can better tolerate

the emergency procedures if such become necessary. The aged patient, even with advanced degenerative disease processes, when carefully evaluated and prepared for surgery, may be operated upon with a mortality of less than 2 per cent. In acute cases the improvements in all types of preoperative and postoperative care of biliary tract patients have produced notable reductions in mortality and complication rates in the younger age groups; but in the aged the mortality for such procedures remains above 5 per cent.

This fact should prompt the surgeon to be less hesitant to employ cholecystostomy (under local anesthesia) in the aged patient with degenerative disease processes who has acute cholecystitis. Thus in effect an emergency situation is converted into an elective surgical problem. In most instances, an elective cholecystectomy should be performed several months following the cholecystostomy. It has been accomplished in all instances without mortality in this group, i.e., the postcholecystostomy, cholecystectomy. The impression that acute biliary tract conditions become a progressively increasing menace to the aged patient is unavoidable in consideration of these data. Prophylactic cholecystectomy in the younger patient with calculus cholecystitis would seem of increasing worth in this era in which the life expectancies of the aged are progressively increasing.

SUMMARY

The age factor in the surgical treatment of biliary tract disease is analyzed by using an experience with a series of 4,050 patients treated surgically in this medical center. Among patients under 50 years of age the rate of fatal complications in nonmalignant disease of the biliary tract has been 0.65 per cent. Among patients 50 to 64 years old this rate is 2.5 per cent; and among those patients over 65 years of age it is increased to 6.7 per cent. For elective surgical procedures the difference in mortality is not significant. The high mortality rate among aged patients occurs following emergency surgery. Thus the complications of acute cholecystitis in the aged patient with degenerative disease are the chief factor in the operative risk. Surgery should be done in older patients with acute cholecystitis; but they merit the most meticulous care in surgical management. This includes operation as early as possible in an acute attack before complications such as perforation, stone obstruction, and jaundice appear. Our experience appears to justify the policy of regarding all calculus cholecystitis, whether symptomatic or not, as a potential hazard and an indication for elective cholecystectomy. Unique aspects of biliary tract disease in the aged include: (a) an increased incidence of acute cholecystitis; (b) an increased incidence of choledocholithiasis with larger and more numerous choledochal calculi; (c) the occurrence of acute processes in the biliary tract with minimal signs and symptoms; and (d) the increased incidence of associated biliary tract neoplasia.

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THE MENSTRUAL PATTERN IN HYPERTHYROIDISM AND SUBSEQUENT POSTTHERAPY HYPOTHYROIDISM

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THE ASSOCIATION of hyperthyroidism and the incident change in menstruation, although described previously, is not well recognized. A demonstration of the natural course of certain gynecologic events in a large series of patients with toxic goiter emphasizing menstrual changes before and after definitive therapy should be of interest, therefore, to the endocrinologist, the internist, and the gynecologist. With the intent of establishing the menstrual pattern during thyrotoxicosis and after specific therapy, we have reviewed the clinical histories of 274 premenopausal female patients with authenticated hyperthyroidism treated at the University of California Hospital during the past 15 years.

The fact that a significant proportion of women with toxic goiter became hypothyroid after surgical or other specific treatment presented an opportunity to study the effect of thyroid deficiency on menstruation in the same patients. Individuals with gynecologic disease, significant pelvic operations in the past, or in whom a record of menstrual history was inadequate were eliminated from our study. The age distribution is shown in Table I.

Cases of hyperthyroidism were divided into three categories (Fig. 1): (1) toxic diffuse goiter, including Graves' disease, (2) toxic nodular goiter, and (3) toxic recurrent goiter.

An appraisal of the degree of initial hyperthyroidism seemed necessary for a proper analysis of the problem. In this connection, it is obvious that neither basal metabolic rates nor other laboratory findings alone are sufficient for grading; reference must also be made to the clinical signs and symptoms. The degree of exophthalmos is certainly no guide to the degree of hyperthyroidism. The segregation of our cases into groups of varying degrees of severity was often facilitated by a statement in the record by an experienced senior clinician regarding the degree of hyperthyroidism. In general, however, patients with severe thyrotoxicosis manifested profound weight loss, involvement of nearly all organ systems, agitation, and muscle atrophy. Yet, it should also be recalled that in severe hyperthyroidism, anorexia is not rare. The basal metabolism of such patients is usually in the neighborhood of at least plus 50 per cent. In mild hyperthyroidism the signs are more subtle and fewer functions are involved. The basal metabolic rate in the mild cases in this series was below 25 per cent. Obviously, the moderately severe cases represent intermediate degrees of abnormality. Admittedly, the grading of the degree of hyperthyroidism based solely on clinical records is difficult; nevertheless, when doubt existed, the case was placed in the less severe category. A scientific generalization then was attempted on the basis of recorded observations, and the cases were divided into instances of mild, moderate, and severe toxic goiter. This categorization was accomplished without any reference to the menstrual history.

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TOXIC DIFFUSE GOITER

Two hundred twenty-one cases of toxic diffuse goiter were grouped as follows: mild, 70; moderate, 124; severe, 27.

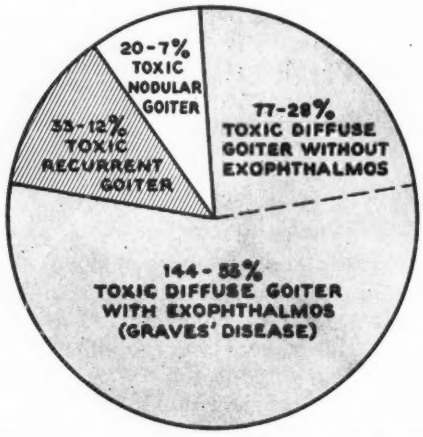

FIG. 1. Hyperthyroidism in 274 patients at the University of California Hospital

A critical review of the menstrual histories of the 70 patients with *mild* toxic diffuse goiter revealed that 35 (50 per cent) had experienced a decrease in amount and duration of menstrual flow, while only 4 (5.7 per cent) described an increase in bleeding during thyroid overactivity. The character of menstruation was unchanged in 34 (44 per cent) of patients in this group. In the *moderate* cases, a menstrual decrease occurred in 75 (60 per cent), an increase occurred in 4 (3.6 per cent), and no change was recorded in 45 (36 per cent). In 27 patients with *severe* toxic diffuse goiter, menstrual decrease occurred in 20 (74 per cent), an increase in 2 (7 per cent), and no change in 5 (18.5 per cent). A representative case is shown in Figure 2.

An almost linear relationship, therefore, was found between the decrease in the amount and duration of the menstrual flow and the associated increase in the severity of toxic goiter (Fig. 3).

TABLE I.—AGE DISTRIBUTION IN 274 WOMEN WITH HYPERTHYROIDISM

Age, yrs.	*Toxic diffuse goiter*	*Toxic nodular goiter*	*Toxic recurrent goiter*
14–19	22	0	0
20–29	91	2	17
30–39	79	11	10
40–46	29	7	6
Total	**221**	**20**	**33**

Although it is not possible to consider the many factors involving fertility from the case histories available, at least 27 (possibly 30) (14 per cent) of the total of 221 patients with toxic diffuse goiter noted the onset of toxic goiter at the time of a pregnancy. None of these patients experienced an eclamptogenic toxemia. The abrupt onset of hyperthyroidism during pregnancy is most striking, as previously recorded (3), and is evident from the records of the women so affected.

TOXIC RECURRENT GOITER

It is often difficult to differentiate between incompletely treated toxic goiter and actual recurrent toxic goiter. We used the criteria of a reasonable period of good health after specific therapy for hyperthyroidism and normal laboratory findings during the interim to distinguish partially treated hyperthyroidism from actual recurrent toxic goiter.

Menstrual aberrations of marked degree are not necessarily expected in a group of this type. Such patients are under careful observation following surgical or other definitive therapy for hyperthyroidism; when they do show signs of recurrent toxicity, treatment is initiated promptly, usually before gross changes occur. Despite this attitude of alertness, however, certain women did report signs and symptoms of toxic goiter, and the occurrence of oligomenorrhea was usually confirmatory of the trend toward toxicity.

Thirty-three (12 per cent) of the entire group of 274 hyperthyroid women were considered to have toxic recurrent goiters. There were 14 instances of mild thyrotoxicosis. Six of these patients reported a decrease in menstrual flow during the interval of recurrent hyperthyroidism. None of the patients described an increase, and 8 recorded no change in the amount and duration of cyclic uterine bleeding. The group of patients with moderately severe toxic recurrent goiter consisted of 18 women, 4 of whom showed a decrease in menstrual

flow; none recalled an increase, and 14 described no change. Only 1 patient was categorized as having severe toxic recurrent goiter, and this woman noted no change in menstrual pattern during the acute phase of brief thyroid exacerbation. Hence, 10 of the 33 patients with toxic recurrent goiter described a decrease in menstrual flow and 23 recorded no change; no woman in this group admitted an increased menstrual flow during a recurrence of thyrotoxicosis. An illustrative case is shown in Figure 4.

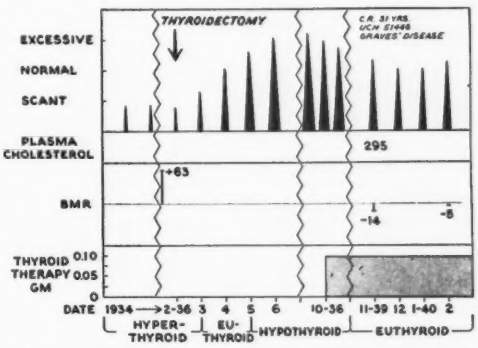

FIG. 2. Mrs. C.R., a 31 year old, white, nulligravida, had suffered from agitation, weight loss, and progressive prominence of the eyes for 2 years. When first examined, an obvious exophthalmic goiter of a severe degree was noted. The initial basal metabolic rate was plus 63 per cent. Routine questioning revealed the history of irregular, scanty 2 day periods for the past 1 to 2 years. The menses prior to this illness had been regular and of moderate amount for 5 to 7 days each month. Subtotal thyroidectomy was accomplished after preparation with Lugol's solution. One month after operation, the patient was considered euthyroid, and 2 months postoperatively the periods became normal. Three months after thyroidectomy, signs and symptoms of hypothyroidism were noted, and the next month menorrhagia and polymenorrhea began. The patient did not report her progressive difficulties until 8 months postoperatively, however, and at this time, severe myxedema was diagnosed. Desiccated thyroid substance, 0.1 gram per day, was immediately prescribed, and the patient became euthyroid. The menstrual flow became and continued normal and regular on this thyroid supplement.

TOXIC NODULAR GOITER

Twenty patients (7 per cent) were included in this category. Of the group of 12 women with mild toxic nodular goiter, 8 described a decrease in menstrual flow, and 4 no change in their periods; no instance of increased menstrual flow or prolongation of bleeding was noted. Of the 6 women with moderate toxic nodular goiter, 3 recalled a decrease, 3 no change, and none recorded excess menstrual bleeding during the acute phase of thyroid illness. The 2 patients with severe toxic nodular goiter both experienced decreased menstrual flow and duration of bleeding.

Thirteen of 20 patients with toxic nodular goiter, then, experienced oligomenorrhea during hyperthyroidism. No woman noted menorrhagia, and 7 reported no change in menstrual function. For representative case, see Figure 5.

Summary. If we combine all grades of severity of thyrotoxicosis in this series and consider the effect of hyperthyroidism upon the menstrual pattern, it becomes apparent that *if* a change does occur, it almost invariably consists of a suppression of the flow in association with oligomenorrhea or amenorrhea or both (Fig. 6).

AMENORRHEA

Our observations on the relationship between amenorrhea and the variations in the syndrome of hyperthyroidism are of especial interest:

No cases of amenorrhea due to hyperthyroidism were recorded in patients who did not also manifest exophthalmos. Of the 144 cases of toxic diffuse goiter with eye signs, amenorrhea was reported by none of the 32 patients in the mildly toxic group, by 7 of the 90 subjects in the moderately toxic group, and by 3 of the 22 patients in the severely toxic group.

Only 1 patient with a toxic recurrent goiter reported amenorrhea while she had a mild re-exacerbation of hyperthyroidism. No patient with toxic nodular goiter in this series had ocular signs, and none had amenorrhea.

Obviously, the increase in the incidence of amenorrhea rises with the severity of the hyperthyroidism. Moreover, a relationship between exophthalmos and amenorrhea is

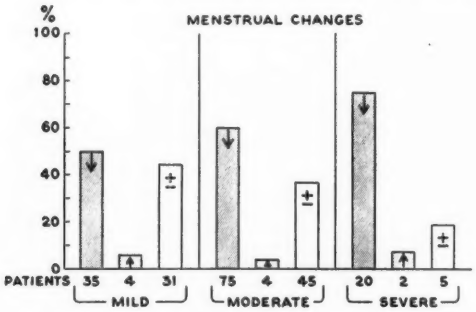

FIG. 3. Toxic diffuse goiter in 221 patients at the University of California Hospital.

suggested because all our patients with amenorrhea had unequivocal exophthalmos.

HYPOTHYROIDISM

Clinically recognizable hypothyroidism occurred in 31 (14 per cent) of the 221 patients with toxic diffuse goiter, regardless of the method of treatment. This incidence compares with the expected occurrence of hypothyroidism (18 per cent) after subtotal thyroidectomy for toxic goiter in this clinic, as reported by Goldman. (The occurrence of thyroid deficiency is lower in the present series, presumably because of the frequent employment of x-ray therapy and radioactive iodine during recent years.) Because of the smallness of the series, no attempt was made to establish the degree of thyroid deficiency.

Eighteen of 31 hypothyroid women noted the occurrence of menorrhagia or polymenorrhea or both during the period of decreased thyroid function subsequent to specific therapy for hyperthyroidism. The remaining 13 women showed no change in menstrual periods from their pretreatment normal after becoming hypothyroid.

Of the group of 14 women who received thyroid and who were followed long enough to note the results of this therapy, the menses returned to normal in 12. One patient continued to suffer from menorrhagia despite thyroid therapy; another woman disclosed a spontaneous recovery from mild hypothyroidism and a resumption of the periods to normal after 2 months without thyroid medication.

Of the 33 patients in the group with toxic recurrent goiter, 3 became hypothyroid after therapy. Two of these 3 reported menorrhagia and both experienced correction of the menstrual pattern to normal following treatment with desiccated thyroid. One woman showed no change in menstrual periods either before or after thyroid supplement.

Of the patients with toxic nodular goiter, 2 became hypothyroid after initial therapy. Only 1 of these developed menorrhagia, however, and this complication was corrected by thyroid therapy alone.

Summary. Hypothyroidism, as noted in the present series, usually was associated with menorrhagia or polymenorrhea, *if* a menstrual change occurred. Amenorrhea was not a problem in these women who became thyroid deficient after treatment for toxic goiter.

DISCUSSION

As we have shown, excess thyroid stimulation often causes a reduction of menstrual bleeding, and thyroid deficiency is associated with menorrhagia. The salutary effect of thyroid substance, particularly the correction of menorrhagia, polymenorrhea, and amenorrhea, in women with demonstrable hypothyroidism is well known. The use of desiccated thyroid in the treatment of any and every functional irregularity of uterine bleeding is, however, time honored. Although it is known that thyroid therapy is often useful in the control and correction of this abnormal bleeding, the reason why it is effective is, at the present time, still unknown.

Generally speaking, specific hormonal connections between the thyroid and the gonads have been denied, even though clinical data indicate a close correlation between thyroid and ovarian functions. It is probable that the thyroid affects the ovary indirectly through the mediation of the pituitary.

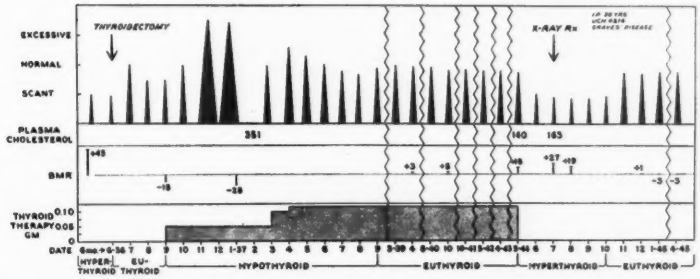

FIG. 4. Mrs. I.P., a 30 year old, white, parous woman, was first examined in 1936. She gave a history of excessive weight loss, tremor, and tachycardia for 6 months. The menses, hitherto regular each month for a moderate 4 to 5 day flow, had checked markedly during the past half year. A basal metabolic rate was reported as plus 45 per cent, and a diagnosis of moderately severe Graves' disease was made. A subtotal thyroidectomy was carried out after preparation with iodides. One month postoperatively a normal period was recorded; 3 months postoperatively the basal metabolic rate was minus 18 per cent, and signs and symptoms of hypothyroidism were apparent. She was treated with thyroid substance, 0.05 gram daily. This dose proved to be inadequate, inasmuch as 7 months after operation the basal metabolic rate was minus 28 per cent, at which time the plasma cholesterol was reported to be 351 milligrams per cent. Meanwhile, the menses became profuse and prolonged. Desiccated thyroid was promptly increased to 0.1 gram daily, and after 2 months on this medication the patient was noted to be euthyroid on thyroid treatment. The periods returned to normal concomitantly and remained constant for 7 months, whereupon clinical signs and symptoms of toxic goiter recurred. Thyroid medication was discontinued, but the basal metabolic rate remained elevated at plus 27 per cent and the periods became scanty and irregular. Multiple sclerosis was also diagnosed and x-ray therapy was chosen rather than another thyroidectomy. A dosage of 2,700 roentgens was administered in three courses over 4 months. The patient became euthyroid in 4 months after initiation of roentgen therapy, and her basal metabolic rate fell to normal levels. The menses similarly resumed a normal pattern, and no further thyroid or gynecologic problems were reported.

The role of the thyroid in reproductive function has been emphasized for many years. Naturally, much of the investigation of this problem has been done in experimental animals. One hesitates to extrapolate too freely, but certain conclusions derived from animal experimentation about the interrelationship between pituitary, thyroid, and ovary can be applied to women.

A brief study of menstruation in the Macaca mulatta monkey as it is related to thyroid activity was reported by Burford and associates. They found that thyroid ablation caused no change in the threshold of the ovarian hormone required to induce menstruation (in the ovariectomized animal). Engel described prolonged amenorrhea in the rhesus monkey after thyroidectomy, although why this occurred was not determined. He found that thyroid substance would allow resumption of the periods and that as little as one course of treatment would induce two or three apparently normal periods.

Gillman and Gilbert made elaborate studies of hypothyroidism and the associated menstrual changes in the baboon. They indicated that in the ape with hypothyroidism, a widespread metabolic disturbance occurs which involves not only a modified gonadotrophic production and pituitary rhythm, but also an alteration in the responsiveness of the ovaries to pituitary hormones. In these monkeys amenorrhea is related to all grades of gonadal dysfunction, ranging from ovarian failure to hyperestrinism. Even in the occasional case where a corpus luteum did form, a normal secretory endometrium failed to develop. Thyroid substance, however, was capable of

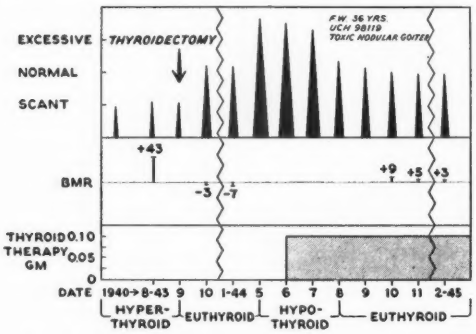

FIG. 5. Mrs. F.W., a 36 year old, white nulligravida, had noted the progressive development of irritability, tremor, and unilateral enlargement of the neck over a 3 year period. The menses during this time had become irregular and scanty, whereas prior to the illness they had been regular and moderate in amount. She finally sought medical counsel; the basal metabolic rate was plus 43 per cent, and a diagnosis of toxic nodular goiter of moderately severe type was made. Excision of the thyroid nodule was effected after iodine therapy. One month later the basal metabolic rate was minus 3 per cent, and the patient was clinically euthyroid. The menstrual periods became normal. Eight months after operation, however, obvious signs and symptoms of thyroid deficiency became apparent. At the same time menorrhagia of a severe degree was described. She was given 0.1 gram of thyroid substance per day, and after 2 months the periods resumed normal character and regularity. The basal metabolic rate returned to normal range, and the patient continued to be euthyroid on thyroid medication.

restoring normal menses in these hypothyroid animals irrespective of the nature of the menstrual disorder. Regrettably, no similar study of hyperthyroidism in the Primates is as yet available.

Toxic goiter occurs 10 times more frequently in women than in men. In view of this very definite preponderance, the implication that the increased incidence of hyperthyroidism may be related to the female endocrine system is not unexpected. In this regard the physiologic enlargement of the thyroid at puberty, with pregnancy, with parturition and at the menopause is often noted.

The nature of the menstrual abnormality is neither evident from this nor other studies of hyperthyroidism and hypothyroidism. Nevertheless, we can probably assume the occurrence of numerous anovulatory cycles, particularly in the women in our series with long episodes of amenorrhea and with polymenorrhea. The fact that many younger women described "hot flashes," particularly during oligomenorrhea and amenorrhea, with later relief of this symptom when normal menstruation resumed after therapy for toxic goiter, suggests excess pituitary gonadotrophic hormone effect.

Ovarian failure seems probable in many of the hypothyroid women with acyclic bleeding and amenorrhea, as suggested by Goldsmith and associates. Their statement that the myxedematous patient is subject to "continued estrogen-effect on the endometrium, but without ovulation and the additional progesterone effect which characterizes the normal cycle" may be true. This conclusion, however, is not particularly illuminating, inasmuch as the same might be said of hyperthyroid patients, when we recall that amenorrhea may result from excessive estrogen production, diminished estrogen production, or prolonged corpus luteum effect.

An excessive or persistent concentration of unopposed estrogen is invariably followed by abnormal uterine bleeding. Desiccated thyroid, in addition to its specific dynamic effect of improving the utilization of estrogenic hormone, appears to prevent excessive concentration of estrogen in the endometrium by increasing its elimination. Hence, thyroid substance will be theoretically useful in certain instances of dysfunctional uterine bleeding where anovulation is the rule rather than the exception. Actually, in Buxton and Vann's sterility-endocrine clinic series, 62 per cent of a group of women who reported hypomenorrhea and all of those describing hypermenorrhea were cured after thyroid medication alone.

The finding that all our patients with amenorrhea had exophthalmos is intriguing. Could it be that the more severe the thyrotoxicosis, the greater the stimulation by the pituitary, hence the lower the gonadotrophic production and the greater the likelihood of amenorrhea? The presence or absence of

exophthalmos might constitute a clinical dividing sign between a thyrotoxicosis which lowers gonadotrophic hormone production to amenorrheic levels and that which merely results in oligomenorrhea.

The decrease in menstrual bleeding in hyperthyroidism could be caused by a suppression of pituitary gonadotrophins as a result of a high level of thyroid activity. On the other hand, excessive flow is often associated with hypothyroidism and this might be attributed to gross production of pituitary gonadotrophins following dissipation of thyroid hormones.

These explanations unfortunately do not explain why hyperthyroidism and hypothyroidism are associated with amenorrhea as well as with oligomenorrhea, nor why hypothyroid patients with menorrhagia or polymenorrhea improve after the administration of desiccated thyroid. A fair assumption is that gonadotrophins are depressed in both excessive and subnormal thyroid function and, moreover, that failure of ovulation is fundamental in both amenorrhea and in metropathica hemorrhagica.

These and other observations linking thyroid and gonadal function do not necessarily imply a single causal relationship. Thyrotoxicosis, for example, exerts a profound effect upon tissue demands for all elements concerned with metabolism. Certainly, greater quantities of vitamins are required by rapidly changing tissues such as the ovary and endometrium for proper function during thyrotoxicosis. This may also be true of certain hormones, such as estrogen and progesterone. During hypothyroidism the function of the ovary and the endometrium, and of other tissues as well, is reduced. This concept is important, we believe, inasmuch as we are not required to invoke a purely direct endocrine explanation for menstrual aberration in hyperthyroidism or hypothyroidism, despite the demonstration of certain thyroid-ovarian relationships. It may very well be that menstrual changes are actually secondary to profound alterations in metabolism and

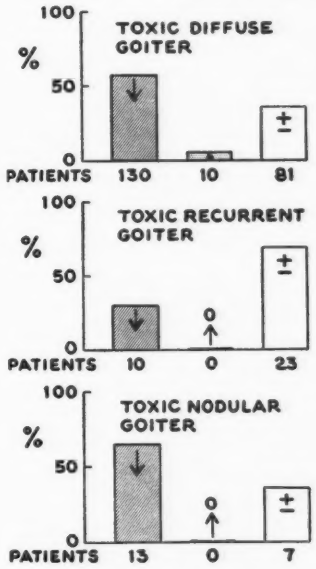

FIG. 6. Menstrual pattern in hyperthyroidism in 274 patients at the University of California Hospital.

that the degree of deviation is related to the extent of thyroid dysfunction.

Irrespective of the theory involved, however, the rapid rebound to normal menstrual function in the definitely premenopausal woman successfully treated for either hyperthyroidism or hypothyroidism despite long debility is most striking. This return within several months of treatment is particularly well demonstrated by the type and rhythmicity of the periods which reflect the success or failure of therapy.

SUMMARY AND CONCLUSIONS

1. The effect of hyperthyroidism and its treatment on the menstrual pattern was studied in 274 premenopausal women.

2. This group was divided into 144 patients with Graves' disease (53 per cent), 77 instances of toxic diffuse goiter without exophthalmos (28 per cent), 33 women with toxic recurrent goiter (12 per cent), and 20 individuals diagnosed as having toxic nodular goiter (7 per cent).

3. Toxic diffuse goiter was found to be associated with a decrease in the amount

and duration of the menstrual flow in 130 patients (58.8 per cent), an increase in 10 (4.5 per cent), and no change in 81 (36.7 per cent). A similar menstrual experience was recorded by patients with toxic recurrent and toxic nodular goiter.

4. A suppression in the amount and duration of uterine bleeding almost invariably occurs in women who suffer from toxic goiter, *if* a change is noted. Successful definitive medical or surgical therapy is followed in several months by the resumption of normal menstruation in the great majority of patients.

5. In this series amenorrhea prior to specific therapy for toxic goiter was noted only in the presence of exophthalmos. Twenty-one women were so affected, all of whom had toxic diffuse goiter.

6. In at least 27 (14 per cent) of our patients the onset of hyperthyroidism occurred during pregnancy, but none of these women suffered from eclamptogenic toxemia in that particular gestation.

7. Clinical hypothyroidism occurred in 31 (14 per cent) of the total number of patients with toxic goiter who were treated.

8. Eighteen patients with posttherapy hypothyroidism noted menorrhagia or polymenorrhea; most of these had experienced oligomenorrhea during their hyperthyroid state. No individual revealed a decrease in menstrual flow or amenorrhea during the time of abnormally low thyroid function.

9. Hypothyroidism as a complication of treatment of toxic goiter is usually associated with menorrhagia or polymenorrhea, if a change is recorded. Normal menstruation generally follows 1 to 2 months of treatment with desiccated thyroid alone.

10. A review of certain details regarding pituitary-thyroid-ovarian relationship in menstruation is presented. Hormonal and nutritional mechanisms which may be theoretically responsible for abnormal uterine bleeding as it complicates toxic goiter and hypothyroidism are described.

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RENAL FUNCTION DURING CONTROLLED HYPOTENSION WITH HEXAMETHONIUM AND FOLLOWING NOREPINEPHRINE

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SINCE CONTROLLED HYPOTENSION for certain surgical procedures has gained greater usefulness through the employment of ganglionic blocking agents, it seemed wise to evaluate the effect of this procedure on the kidney. The various operations in which controlled hypotension offers the most benefit are frequently lengthy procedures. The custom in most clinics is to allow a gradual increase in blood pressure on completion of the operation (in order to avoid reactive hemorrhage) which further extends the hypotensive period. Hence, fluid and electrolyte excretion during a protracted hypotensive period are factors of importance. The primary purpose of the present report was to study the effect of blood pressure reduction on glomerular filtration rate and on the excretion of water and electrolytes and to compare these responses to those obtained when the blood pressure is elevated to or above the control levels with norepinephrine.

METHODS

Observations on renal function and on water and electrolyte excretion were made on 11 normotensive patients without a history or clinical evidence of renal disease. The patients ranged in age from 17 to 48 years. Only 1 of the patients had an elevated blood pressure (Patient 9). This elevation was probably a result of the excitement associated with having the renal function tests performed since the pressure was not elevated prior to the day of the study and it returned to normotensive levels soon after the patient returned to the ward. Glomerular filtration rate was measured with inulin. Renal plasma flow was estimated by the clearance of para-aminohippurate. Mean blood pressure was measured by direct intra-arterial manometry. Arterial blood collected through a manifold was used for all analyses. Methods and techniques employed have been described previously (1, 2). All observations were made in the supine position. After suitable control observations (3 successive 10 minute collection periods) were obtained, the hexamethonium was administered by continuous intravenous infusion in a concentration of 0.5 to 2 milligrams per milliliter of 5 per cent glucose in distilled water. The rate of the infusion depended on the blood pressure response. The initial blood pressure reduction, which was usually observed after 3 to 10 milligrams of hexamethonium were administered, was more marked than that observed after hemodynamic stabilization. After blood pressure stabilization occurred, a "floor" in the blood pressure was obtained, beyond which it was difficult to lower the pressure, except by very rapid infusion with which procedure it was often possible to lower the mean blood pressure an additional 10 to 20 millimeters of mercury. After the initial induction period, the drug was usually administered at the rate of 2 to 8 milligrams per minute. The maximum amount of hexamethonium administered was 1,500 milligrams over a 4 hour period. The average was 250 milli-

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TABLE I.—RENAL HEMODYNAMIC EFFECT OF BLOOD PRESSURE REDUCTION WITH HEXAMETHONIUM

Patient	Mean blood pressure, mm./Hg					Renal blood flow, ml./min.					Renal vascular resistance					Hematocrit				
	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
1. C.E.	104	80	82	82	—	715	698	632	650	—	.15	.11	.13	.13	—	48	48	44	44	—
2. C.S.	105	68	60	56	—	1598	688	1084	1147	—	.07	.10	.06	.05	—	44	44	45	45	—
3. R.V.	78	55	64	63	—	1058	269	641	856	—	.07	.20	.10	.07	—	35	35	36	36	—
4. R.H.	100	62	59	69	—	1390	905	1658	1329	—	.07	.07	.04	.05	—	49	45	47	44	—
5. J.M.	108	73	69	64	61	997	390	910	1131	1178	.11	.19	.08	.06	.05	41	39	33	33	35
6. P.W.	88	70	71	63	66	1073	1412	1302	745	1575	.08	.05	.05	.08	.04	40	40	40	40	40
7. J.S.	85	62	58	60	58	1098	1092	949	1064	1542	.08	.06	.06	.06	.04	51	51	51	44	47
8. L.P.	86	52	53	55	58	1383	1879	1393	1205	1086	.06	.03	.04	.05	.05	46	44	44	41	41
9. J.M.	131	86	69	64	63	661	530	598	939	730	.20	.16	.12	.07	.09	41	40	39	39	39
Mean	98	68	65	64	61*	1108	874	1019	1007	1222*	.10	.11	.08	.07	.05*	44	43	42	41	40*
Per cent of control	—	69	66	65	61	—	79	92	91	117	—	110	80	70	45	—	98	95	93	91
P Value<‡	—	.01†	.01†	.01†	.01†	—	.20	.40	.30	.30	—	.50	.10	.10	.05†	—	.50	.50	.05†	.20

C —Control (average of 3–10 minute periods).
D_1—First period after blood pressure reduction with hexamethonium.
D_2—Average of 2–10 minute periods after blood pressure reduction for 1 hour.
D_3—Two hours after hexamethonium (average of 2–10 minute periods).
D_4—Three hours after haxamethonium (average of 2–10 minute periods).

$$\text{Renal blood flow} = \frac{\text{Renal plasma flow}}{1 - \text{Hematocrit}}$$

$$\text{Renal vascular resistance} = \frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$$

*Control values for same patients were MBP = 100; RBF = 1042; RVR = .11; hematocrit = 44.
†Statistically significant.

$$t_{\bar{x}} = \sqrt{\frac{N(N-1)}{Sx^2}}$$

TABLE II.—EFFECT OF BLOOD PRESSURE REDUCTION WITH HEXAMETHONIUM ON WATER AND ELECTROLYTE EXCRETION

Patient	Glomerular filtration rate, ml./min.					Urine volume, ml./min.					Plasma sodium mEq./liter	Plasma potassium mEq./liter	Sodium excretion, μEq./liter					Potassium excretion, μEq./liter				
	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	C	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
1. C.E.	92	77	88	87	—	1.0	0.6	0.6	0.4	—	142	4.92	39	4	5	7	—	94	52	63	76	—
2. C.S.	111	80	75	78	—	4.2	7.6	0.4	0.4	—	136	5.80	214	36	9	8	—	66	23	36	37	—
3. R.V.	112	58	85	100	—	0.6	0.1	0.4	0.4	—	143	5.98	34	4	2	4	—	39	16	19	26	—
4. R.H.	134	119	128	116	—	1.6	0.7	0.7	0.7	—	141	7.55	100	10	30	36	—	56	80	94	90	—
5. J.M.	142	76	129	144	122	1.0	0.6	0.2	0.4	0.2	150	5.10	76	16	13	17	13	39	18	70	78	60
6. P.W.	165	168	138	89	107	0.9	0.2	0.9	0.4	0.3	138	6.60	117	66	90	7	10	61	49	51	17	71
7. J.S.	109	78	76	85	100	2.9	0.9	0.7	1.1	1.2	142	6.20	236	46	33	86	167	73	47	46	62	90
8. L.P.	87	127	65	85	90	5.1	0.5	0.7	0.6	0.8	146	4.85	89	35	30	13	16	52	10	66	77	86
9. J.M.	67	43	39	49	44	10.2	1.0	1.1	0.8	0.6	142	4.27	36	6	3	9	4	86	65	52	62	63
Mean	113	92	91	93	93*	3.1	1.4	0.6	0.6	0.6*	142	5.70	105	25	24	21	42*	63	40	55	58	74*
Per cent of control	—	81	81	82	82	—	45	19	19	15	—	—	—	24	23	20	38	—	63	87	92	117
P Value <	—	.01†	.01†	.02†	.10	—	.20	.05†	.05†	.20	—	—	—	.01†	.01†	.01†	.01†	—	.01†	.50	.50	.30

C —Control (average of 3–10 minute periods).
D_1—First period after blood pressure reduction with hexamethonium.
D_2—Average of 2–10 minute periods after blood pressure reduction for one hour.
D_3—Two hours after hexamethonium (average of 2–10 minute periods).
D_4—Three hours after hexamethonium (average of 2–10 minute periods).
*Control value (mean) for these same patients: GFR = 114 ml./min.; U.V. = 4.0 ml./min.; sodium excretion = 111 μEq./min.; potassium excretion = 62 μEq./min.
†Statistically significant.

grams over a 3 hour period. Observations on renal function were made on 9 patients for successive 10 minute periods during the first hour of hypotension, and then for two 10 minute periods after 2 hours and again after 3 hours of hypotension in 5 patients.

Following the hypotensive period, the hexamethonium was infused at the same rate as previously but the blood pressure was elevated to or above the control levels by a continuous intravenous infusion of norepinephrine.[1] Collections for 2 consecutive 10 minute periods were then made. Determinations of renal blood flow, glomerular filtration rate, and the excretion rates of water, sodium, and potassium were determined.

RESULTS

Following the initiation of the hexamethonium infusion, the blood pressure usually

[1]Norepinephrine was not administered to Patients 3 to 5 but was given to 2 additional patients (after 1 hour of blood pressure reduction) who were not included in the group of patients in whom the blood pressure was reduced for 2 hours or more.

TABLE III.—RENAL HEMODYNAMIC RESPONSE TO NOREPINEPHRINE AFTER GANGLIONIC BLOCKADE WITH CONTINUOUS INFUSION OF HEXAMETHONIUM

Patient	Mean blood pressure, mm./Hg				Renal blood flow, mm./min.*				Renal vascular resistance‖				Hematocrit		
	C	H	N_1	N_2	C	H	N_1	N_2	C	H	N_1	N_2	C	H	N_2
1. C.E.	104	82	132	126	715	650	655	555	.15	.13	.20	.23	48	44	44
2. C.S.	105	56	95	89	1598	1147	1063	1096	.07	.05	.09	.08	44	45	43
6. P.W.	88	66	121	128	1073	1575	1500	1017	.08	.04	.08	.13	40	40	40
7. J.S.	85	58	116	108	1098	1542	1190	1118	.08	.04	.10	.10	51	47	51
8. L.P.	86	58	115	114	1383	1086	1291	1566	.06	.05	.09	.07	46	41	42
9. J.M.	131	63	148	143	661	730	846	637	.20	.09	.17	.22	41	39	41
10. J.R. f#	84	58	119	135	1145	631	1281	746	.07	.09	.09	.18	36	33	37
11. H.M.#	77	66	112	114	1096	872	738	758	.07	.08	.15	.15	46	43	45
Mean	95	63	120	120	1096	1029	1071	937	.10	.07	.12	.15	44	42	43
Per cent of control	—	66	126	126	—	94	98	85	—	70	120	150	—	95	98
P Value <	—	.01†	.01†	.01†	—	.50	.50	.10	—	.05†	.20	.01†	—	—	—
P Value <*	—	—	.01†	.01†	—	—	.50	.50	—	—	.01†	.01†	—	—	—

Mean blood pressure = Direct intra-arterial manometry.

*—Renal blood flow = $\frac{\text{Renal plasma flow}}{\text{1-Hematocrit}}$

‖—Renal vascular resistance = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$

C—Control.

H—During hexamethonium infusion, 2 to 3 hours after initial reduction in blood pressure.

N_1—First period after norepinephrine infusion started.

N_2—Second period after norepinephrine infusion started.

#—Norepinephrine administered one hour after initial reduction in blood pressure with hexamethonium.

f—Hexamethonium plus Pendiomide administered prior to norepinephrine.

†—Statistically significant.

*—Period H (3 hour observations after blood pressure reduction) used for comparison rather than control period (C) before blood pressure reduction.

TABLE IV.—EFFECT OF NOREPINEPHRINE ON GLOMERULAR FILTRATION RATE AND RENAL PLASMA FLOW WHEN THE BLOOD PRESSURE WAS PREVIOUSLY REDUCED WITH HEXAMETHONIUM

Patient	Glomerular filtration rate, ml./min.				Renal plasma flow, ml./min.				Filtration fraction‖			
	C	H	N_1	N_2	C	H	N_1	N_2	C	H	N_1	N_2
1. C.E.	92	87	88	84	372	364	367	311	.25	.24	.24	.27
2. C.S.	111	78	91	104	895	631	606	625	.12	.12	.15	.17
6. P.W.	165	107	185*	122	644	945	900	610	.26	.11	.21	.20
7. J.S.	109	100	106	89	538	817	583	548	.20	.12	.18	.16
8. L.P.	87	90	110	141	747	641	749	908	.12	.14	.15	.16
9. J.M.	67	44	87	62	390	445	423	376	.17	.10	.21	.16
10. J.R. f#	115	65	158*	89	733	423	807	470	.16	.15	.20	.19
11. H.M.#	117	94	101	115	592	497	406	417	.20	.19	.25	.28
Mean	108	83	116	101	614	595	605	533	.19	.15	.20	.20
Per cent of control	—	77	107	94	—	97	99	87	—	79	105	105
P Value <	—	.02†	.40	.50	—	.50	.50	.20	—	.10	.50	.50
P Value <*	—	—	.05†	.05†	—	—	.50	.40	—	—	.01†	.01†

C—Control.

H—During hexamethonium infusion, 2 to 3 hours after initial reduction in blood pressure.

N_1—First period after norepinephrine infusion started.

N_2—Second period after norepinephrine infusion started.

*—Excessively high value may be due to washout resulting from sudden increase in urine volume.

†—Statistically significant change.

*—Period H (observations made after blood pressure reduction) used for comparison rather than control period (C) before blood pressure reduction.

#—Norepinephrine administered 1 hour after initial reduction in blood pressure with hexamethonium.

f—Hexamethonium plus pendiomide administered prior to norepinephrine.

‖—Filtration fraction = $\frac{\text{Glomerular filtration rate}}{\text{Renal plasma flow}}$

decreased to hypotensive levels within 5 to 10 minutes (Table I). Maximum reduction was obtained within 20 minutes. The average mean blood pressure for the group of 9 patients was reduced from 98 to 68 millimeters of mercury within 10 minutes (D′) which was a highly significant response ($p<0.01$). The average pressure remained within this range for the entire period of study ($p<0.01$). Those patients who obtained the best initial reduction in blood pressure continued to obtain approximately the same response and those patients who were least responsive initially continued to be so throughout the study.

Although the average renal blood flow for the group was initially reduced to 79 per cent of the control values, this was such an erratic response that it was not statistically significant ($p<0\ 20$). Even those patients

TABLE V.—EFFECT OF NOREPINEPHRINE ON CREATININE CLEARANCE, WATER AND ELECTROLYTE EXCRETION AFTER GANGLIONIC BLOCKADE BY A CONTINUOUS INFUSION OF HEXAMETHONIUM

Patient	Urine volume, ml./min.				Plasma sodium, mEq./L.	Sodium excretion μEq./min.				Plasma potassium mEq./L.	Potassium excretion μEq./min.				Creatinine clearance ml./min.			
	C	*H*	N_1	N_2	*C*	*C*	*H*	N_1	N_2	*C*	*C*	*H*	N_1	N_2	*C*	*H*	N_1	N_2
1. C.E.	1.0	0.4	0.5	0.6	142	39	7	5	10	4.9	94	76	85	76	92	100	88	92
2. C.S.	4.2	0.4	0.4	0.4	136	214	8	15	25	5.8	66	37	36	36	109	69	84	108
6. P.W.	0.9	0.3	1.6	3.3	138	117	10	110	121	6.6	61	71	155	171	96	89	147	149
7. J.S.	2.9	1.2	1.2	0.8	142	236	167	150	140	6.2	73	90	76	48	93	91	114	107
8. L.P.	5.1	0.8	1.4	3.1	146	89	16	121	23	4.9	52	86	130	150	—	—	—	—
9. J.M.	10.2	0.6	12.0	7.9	142	36	4	562	241	4.2	86	63	83	94	—	—	—	—
10. J.R.	1.5	0.7	5.6	0.3	136	300	170	700	430	5.9	67	52	122	73	101	69	143	86
11. H.M.	1.3	2.8	1.3	0.8	134	82	38	31	53	4.9	44	47	62	74	104	70	78	127
Mean	3.4	0.9	3.0	2.2	140	139	53	212	130	5.4	68	65	94	90	99	81	109	112
Per cent of control	—	26	88	65	—	—	38	153	94	—	—	96	138	132	—	82	110	113
P Value<	—	.10	.50	.20	—	—	.01†	.50	.50	—	—	.50	.30	.30	—	.10	.50	.30
P Value<*	—	—	.20	.20	—	—	—	.20	.10	—	—	—	.05†	.20	—		.10	.05†

C—Control.
H—During hexamethonium infusion, 2 to 3 hours after initial reduction in pressure.
N_1—First period after norepinephrine infusion.
N_2—Second period after norepinephrine infusion.
†—Statistically significant.
*—See Table IV.

who showed an initial reduction in renal blood flow tended to return to the control values after 1 hour at which time the average for the group was 92 per cent of the control observations ($p<0.40$).

Associated with the reduction in blood pressure, glomerular filtration rate was depressed immediately ($p<0.01$) in 7 out of the 9 patients and usually remained depressed throughout the study (Table II). The reduction in glomerular filtration rate was fairly constant and the change was great enough to remain statistically significant. The reduction in blood pressure was followed by a depression in water ($p<0.05$) and sodium excretion ($p<0.01$) which remained depressed throughout the hypotensive period. In contrast to the effect on sodium excretion, potassium excretion was initially depressed ($p<0.01$) but this gradually returned toward the control levels so that after 2 hours of hypotension it was back to 92 per cent of the control which was not a significant alteration ($p<0.5$). After 3 hours of hypotension potassium excretion increased above the control level.

When the blood pressure was increased to or above the control levels with norepinephrine, renal blood flow was not altered appreciably ($p<0.50$) but renal vascular resistance increased about 20 to 50 per cent ($p<0.01$) above the control level indicating that an equivalent degree of vasoconstriction occurred in the kidney as occurred in the body as a whole (Table III).

As the blood pressure was increased with norepinephrine, glomerular filtration rate approximated the control observations, sometimes being slightly below it and other times being above it (Table IV). This increase in glomerular filtration rate during the administration of norepinephrine was significant ($p<0.05$). When the glomerular filtration rate increased, urine volume and sodium excretion approached the control values, the excretion rates of sodium sometimes exceeding the control observations. Those patients in whom a marked rise in sodium excretion above the control levels occurred, usually showed a reduction during the second period of norepinephrine infusion. These observations indicate that the previously observed reduction in sodium and water excretion associated with the depression in glomerular filtration is secondary to the reduction in blood pressure rather than a direct effect of the ganglionic blocking agent. When norepinephrine is administered to a normotensive individual, it has very little effect either on the glomerular filtration or on the sodium and the water excretion.

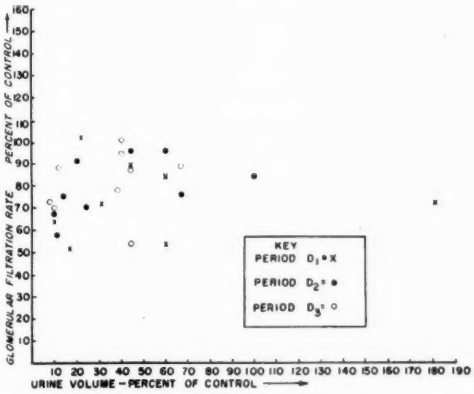

Fig. 1.

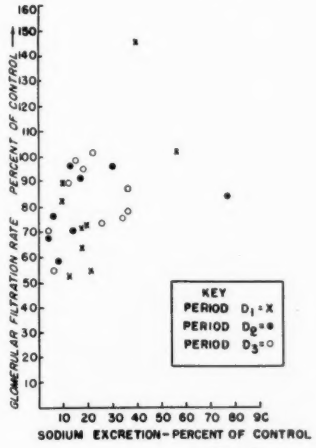

Fig. 2.

FIG. 1. Response to continuous infusion of hexamethonium. Urine volume during hypotension is plotted against glomerular filtration rate expressed in per cent of control observations. Urine volume is depressed out of proportion to the reduction in glomerular filtration rate.

FIG. 2. Response to continuous infusion of hexamethonium. Sodium excretion during controlled hypotension is plotted against glomerular filtration rate expressed in per cent of control observations. Sodium excretion is depressed out of proportion to the reduction in glomerular filtration rate.

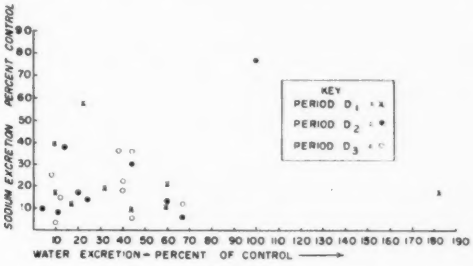

Fig. 3.

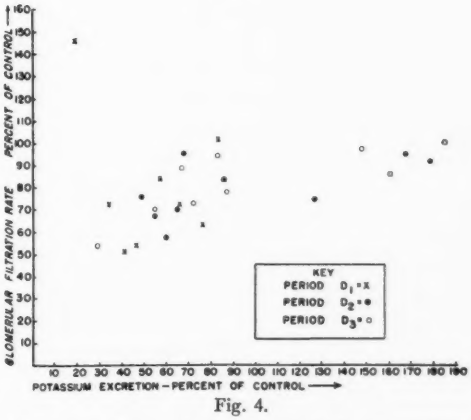
GLOMERULAR FILTRATION RATE PERCENT OF CONTROL
KEY
PERIOD D1 = X
PERIOD D2 = ●
PERIOD D3 = ○
POTASSIUM EXCRETION – PERCENT OF CONTROL

Fig. 4.

FIG. 3. Response to continuous infusion of hexamethonium. Sodium excretion is plotted against water excretion during controlled hypotension. Both are consistently depressed in the same direction.

FIG. 4. Response to continuous infusion of hexamethonium. Potassium excretion is plotted against glomerular filtration rate during controlled hypotension. Both are expressed in per cent of control observations for the individual subjects. Initially both glomerular filtration rate and potassium excretion are reduced proportionately. However, as hypotension continues, potassium excretion tends to return to or above the control observations irrespective of a continued depression of glomerular filtration rate.

DISCUSSION

These studies indicate that adequate renal vasodilatation occurs when the blood pressure is reduced to hypotensive ranges by the use of continuous infusions of hexamethonium. Although renal blood flow is slightly depressed initially, it rapidly returns toward the control levels. However, glomerular filtration rate remains somewhat depressed. This reduction in glomerular filtration is apparently due to inadequate perfusion pressure and is enough to cause sodium and water retention over a period of 2 to 3 hours, although the amount of sodium and water retention is far out of proportion to the reduction in glomerular filtration rate (Figs. 1 and 2). The reduction in both sodium and water excretion seems to be proportional

and is quite consistent (Fig. 3). This response should probably be borne in mind when large amounts of fluids are administered during surgical procedures employing controlled hypotension. Referring to Figure 4 it is quite apparent that potassium excretion is at first depressed but that the excretion rate tends to increase as hypotension is maintained. This occurs even though the urine volume might be reduced farther.

The continued depression of glomerular filtration rate and water and sodium excretion throughout the period of hypotension is probably not related to the ganglionic blocking agent per se but is rather a result of the reduction in blood pressure. This concept is supported by the observations showing a sharp increase in these functions toward the control level when norepinephrine is infused and the blood pressure elevated to normotensive ranges. Since hexamethonium continued to be infused at the same time the norepinephrine was administered, there was no alteration of the degree of ganglionic blockade during this period.

SUMMARY AND CONCLUSIONS

Observations have been made on the renal effects of controlled hypotension with hexamethonium for periods of 2 to 3 hours. Although renal blood flow is slightly depressed in some patients, compensatory renal vasodilatation rapidly occurs and renal blood flow returns to control levels. However, glomerular filtration rate is depressed initially and continues to be depressed as long as the infusion of hexamethonium is continued and the blood pressure remains lowered. The depressed glomerular filtration rate is associated with both an initial and sustained decrease in water and sodium excretion as long as the blood pressure remains reduced. Potassium excretion is also depressed initially, but this slowly returns to control levels despite the continued reduction in blood pressure and glomerular filtration rate.

When the blood pressure is elevated with norepinephrine during continued infusion of hexamethonium, glomerular filtration rate returns toward the control levels. This is associated with a parallel increase in sodium and water excretion.

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LIGATION OF THE HEPATIC ARTERY IN EXPERIMENTAL CIRRHOSIS OF THE LIVER WITH PORTAL HYPERTENSION

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PORTAL HYPERTENSION is being vigorously studied by many investigators, but opinions vary as to the best method so far available for treatment of this condition in man. It is difficult to get clear-cut answers to this problem in the experimental animal. The induction of portal cirrhosis with a concomitant portal hypertension in a laboratory animal that will prove suitable for testing operative procedures is difficult, for not only must a true Laennec-like cirrhosis be produced, but the animal must also be maintained in sufficiently good health to withstand subsequent major surgical procedures.

We have tested the effect of hepatic arterial ligation on experimental portal hypertension caused by a Laennec-type cirrhosis in the dog. The current interest and conflicting reports about hepatic artery ligation as an effective treatment for portal hypertension point out the need for such experimental work.

Investigators have in general employed two methods to produce liver cirrhosis in animals simulating the Laennec-type in man. The first consists of deficient diets, as used by Rich, Fouts, Chaikoff, and others. Animals prepared in this manner are unsatisfactory for long term experiments in which operative procedures are required because the animals will not tolerate severe trauma. The second method is that of using hepatotoxic agents. The most widely used hepatotoxic agent has been carbon tetrachloride. Much of the work with this substance has been done by Bollman and Mann who showed that a cirrhosis of the liver practically indistinguishable from that occurring in man could be induced in dogs by repeated doses of carbon tetrachloride through a stomach tube (5, 6, 7). These investigators reported that with a well balanced diet about 6 months was needed to produce cirrhosis. In the experiments to be reported the method of Bollman and Mann was used because of its simplicity and effectiveness. Acceleration of the development of cirrhosis was attempted in a few dogs by combining carbon tetrachloride administration with surgically induced chronic passive venous congestion of the liver. Portal venous stasis was accomplished by the Stone and Murphy technique in which the thoracic inferior vena cava was partially constricted by a cuff of tantalum mesh and cellophane.

After establishing by repeated liver biopsy the development of hepatic cirrhosis of moderately advanced degree, the portal pressures were determined and the hepatic and gastroduodenal arteries ligated and divided. Surviving animals were later sacrificed after again measuring the portal pressures.

METHOD

Twenty-three mongrel dogs ranging in weight from 10 to 20 kilograms were placed on a diet consisting of 7 parts canned horse meat, 5 parts Pratt's dog food, and occasional fresh vegetable supplements. One and one-half grams of sulfamerazine were given by mouth daily for 5 days and 20 cubic centimeters of distemper serum once weekly for 3 weeks. Six of the 23 dogs had partial vena cava ligations as described before beginning carbon tetrachloride administration. Two cubic centimeters of carbon tetrachloride per kilogram were mixed with an equal

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TABLE I.—RESULTS OF LIVER BIOPSIES

Dog No.	*No. of doses*	*Extent of cirrhosis*	*Liver appearance*	*Splenomegaly*
995	27	Early to moderate	Granular	+
997	28	Early to moderate	Granular	0
1001	28	Moderately advanced	Granular	+
1022	28	Far advanced	Hobnailed	+
1080	27	Early	Granular	+
1189*	26	Far advanced	Granular	+
1235*	12	Moderately advanced	Granular	+

*Dogs with partial ligation of thoracic inferior vena cava.

amount of vegetable oil to increase the evenness of absorption of the agent from the intestinal tract and were given once weekly by stomach tube to the dogs in a fasting state. The carbon tetrachloride was withheld unless the dog was active, again eating, and appeared to have recovered from the previous administration of the drug.

The development of the cirrhotic process was followed by monthly liver biopsies. Initially, these were taken by a Franceen needle but since the samples that were obtained were not entirely satisfactory, laparotomy with liver wedge biopsy was resorted to. This also gave an opportunity to examine the liver grossly, as well as to note the size of the spleen and the development of collateral venous circulation. The dogs which had partial ligation of the thoracic inferior vena cava and developed ascites had abdominal paracentesis performed as needed, with removal of a maximum of 1 liter of fluid at a time.

Liver biopsy sections were prepared with both hematoxylin and eosin, and trichrome stains. When it appeared by gross inspection and microscopic examination that a moderately advanced cirrhosis had developed, the dogs were then operated upon. Under nembutal anesthesia the abdomen was opened through a high midline incision. The portal pressure was recorded by water manometer, the hepatic and gastroduodenal arteries doubly ligated and divided, and the portal pressure again measured before closing the abdomen.

A large mesenteric vein was used to measure portal pressure, for as Douglass and coworkers, Morris and Miller, and others have demonstrated, the normal portal pressure of the dog ranges from 10 to 15 centimeters of water whether measured directly in the portal vein or in a large tributary. When a large tributary vein is used the difference in height from it to the portal vein must be taken into account.

The animals were given 300,000 units of crysticillin immediately following operation and once a day for 5 days in order to protect the liver from gangrene as shown by the studies of Markowitz and associates. Fifteen to 29 days later the surviving animals were again operated upon, portal pressures recorded, and the dogs sacrificed and autopsied.

RESULTS

Of the 23 dogs originally prepared for the experiment, only 7 survived until arterial ligation could be performed. Distemper was responsible for 5 deaths, despite immunization; acute hepatic insufficiency for 6, as proved by postmortem liver biopsy; technical errors for 2 deaths; and other miscellaneous causes for 3 deaths. The 70 per cent mortality shows the difficulties encountered in attempting to maintain dogs in adequate nutrition for a long period while simultaneously inflicting periodic acute liver injury.

In 6 dogs the thoracic inferior vena cava was partially ligated and of these, only 2 survived, for 20 and 33 weeks respectively. It is probably significant that these 2 surviving animals did not develop severe ascites while the 4 that died had considerable ascites and required weekly paracenteses. Hepatic venous stasis obtained by partial caval ligation appears to hasten the development of cirrhosis but undoubtedly affects long term survival unfavorably, particularly when massive ascites develops.

Early liver sections showed widespread necrosis and hemorrhage in the liver with occasional evidence of nodular regeneration and fibroblastic streaking. Later sections showed centrilobular fibrosis, parenchymal disorganization, regenerating nodules, and, eventually, thick fibrous bands intersecting and surrounding liver lobules. The extent of

the cirrhotic process was not uniform in all dogs receiving a similar number of doses of carbon tetrachloride. Indeed, there was in some instances marked variation from a scant fibrosis to a very extensive cirrhosis. Such variables as degree of intestinal absorption and bowel transit time account in large measure for these differences in degree of development of cirrhosis. In Table I is shown for comparison the results of one set of liver biopsies. The liver wedges were taken 7 to 10 days after giving carbon tetrachloride to allow time for recovery from the acute phase of liver injury.

At laparotomy when portal pressures were taken, the spleens in all dogs were found to be increased from one to two times normal size, indicating that portal hypertension had been produced. With the exception of dog No. 1022 whose hobnailed liver is shown in Figure 1, all the livers had taken on a granular appearance of varying texture from coarse to fine.

Dogs No. 1189 and No. 1235, which had partial ligation of the thoracic inferior vena cava, did not develop ascites. As stated, these 2 dogs survived, while 4 others that developed ascites did not. Although all 6 cavae were constricted by at least one-third of their diameters, there appears to be a critical point at which hepatic venous pressure is or is not raised enough to cause ascites to develop. Indeed, Laufman and coworkers found that some dogs never did develop ascites after partial caval constriction and they suggest that the existence of collateral venous channels might explain this variation.

It is interesting to compare the microscopic liver examination of dog No. 1022 after 28 weekly doses of carbon tetrachloride with sections of the liver of dog No. 1235 after only 12 doses (Figs. 2 and 3). Trichrome staining of the section from dog No. 1022 revealed a far advanced cirrhosis with extensive fibrous tissue surrounding and intersecting lobules, while the liver of dog No. 1235 showed an almost equally advanced cirrhotic process. It is possible that this extensive early fibrosis in dog No. 1235 was accelerated by the hepatic venous stasis obtained by thoracic caval constriction.

FIG. 1. Hobnailed liver of dog No. 1022 which had 34 weekly doses of carbon tetrachloride. Discoloration due to postmortem changes. Microscopic sections of far advanced cirrhosis shown in Figure 2.

The hepatic and gastroduodenal arteries were ligated in the 7 surviving dogs. Dog No. 1022, which had the most severe cirrhosis, died 23 hours after operation in what appeared to be hepatic coma. At postmortem its liver appeared pale but intact, and its spleen weighed 600 grams. Dog No. 1001, whose liver was estimated to be next in extent of cirrhosis survived only 3½ days. At autopsy the left lobe of the liver was necrotic and mushy while the right lobe was pale but intact. The remaining 5 dogs survived the ligations. Four of these had appreciable decreases in their portal pressures when measured 12 to 29 days after the division of the hepatic and gastroduodenal arteries. One dog whose portal pressure had decreased immediately after ligation was found to have an increase of 5 centimeters at the time of sacrifice 19 days later. In Table II are tabulated portal pressures before and immediately after the hepatic and gastroduodenal arteries were divided and 12 to 29 days later. Of the 5 dogs surviving arterial ligation it will be seen by comparing Table I with Table II that dogs No. 1189, No. 1235, and No. 1080 with more advanced cirrhosis had

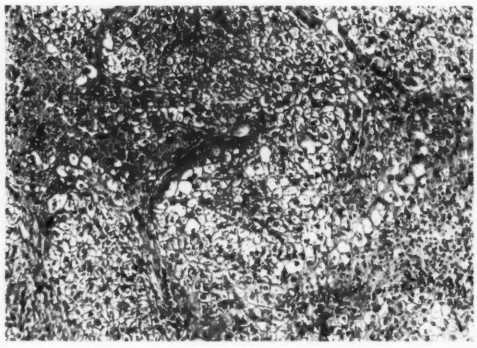

FIG. 2. Section of liver of dog No. 1022 after 28 weekly doses of carbon tetrachloride. Biopsy taken after recovery from acute phase of liver injury. Note extensive fibrosis. × 83.

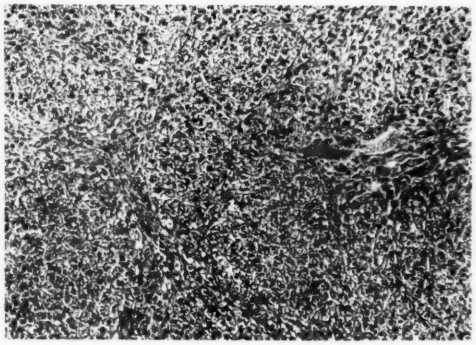

FIG. 3. Section of liver of dog No. 1235 after 12 doses of carbon tetrachloride. Biopsy taken after recovery from acute phase of liver injury. Compare with section shown in Figure 2. × 83.

correspondingly greater portal pressure drops than dogs No. 995 and No. 997 that had not developed as severe a cirrhosis. It is interesting to note that dogs No. 1022 and No. 1001 which had the most advanced cirrhosis survived arterial ligation by only 23 hours and 3½ days respectively.

DISCUSSION

Since Rienhoff (19) first reported "a more simple method of lowering the portal pressure within the portal vein" by ligating the hepatic and splenic arteries, many surgeons have used this operation with variable and often unpredictable results. The rationale for ligation of the hepatic artery in cirrhosis of the liver with portal hypertension is based upon evidence first presented by the research of Herrick many years ago. Herrick found that a definite relationship existed between hepatic arterial pressure and portal vein pressure and that lowering the former resulted in a consequent lowering of the latter. Berman and his co-workers in a series of reports (1–4) have vigorously supported hepatic and splenic arterial ligations for cirrhosis with portal hypertension, and yet in a series of 12 reported ligations for advanced portal cirrhosis, 4 patients died of hemorrhage, 1 the day of operation, 1 three days after operation, and 2 within 5 months of operation.

TABLE II.—PORTAL PRESSURES

Dog No.	*No. of doses*	*Before ligation cm.*	*After ligation cm.*	*At sacrifice cm.*	*Total pressure drop, cm.*	*No. days after ligation*
995	37	26.0	13.8	16.5	9.5	19
997	38	18.5	17.0	13.0	5.5	15
1001	35	55.0	55.0	—	—	—
1022	34	25.2	25.0	—	0.2	—
1080	35	24.0	22.0	13.0	11.0	22
1189*	33	35.5	30.0	16.0	19.5	29
1235*	20	39.5	24.5	16.5	23.0	22

All 5 dogs surviving arterial ligation had decreases in portal pressure ranging from 5.5 to 23.0 centimeters of water when measured 15 to 29 days after operation.
*Dogs with partial ligation of thoracic inferior vena cava.

Rienhoff and Woods have published results of 23 common hepatic artery ligations performed since 1947 (20). They ligated the left gastric artery only in those patients in whom bleeding had occurred. Their overall mortality was 30.4 per cent. Six patients died in the immediate postoperative period, 2 from continuing bleeding. In addition, 1 patient died 3 months later of recurrent hemorrhage from esophageal varices. Of the 23 patients, operation was performed for ascites in 13. In this group 2 died and 11 were improved while of 10 operated upon because of hemorrhage, 5 died.

Rienhoff concludes that ligation of the common hepatic and splenic arteries offers benefit only to patients with ascites and is at best of uncertain value for treatment of bleeding esophageal varices. Experimental evidence supports this view. Berman (1) demonstrated that of 3 dogs on stock rations

made ascitic by constriction of the thoracic inferior vena cava and then treated by hepatic arterial ligation alone, there was a decrease in ascitic fluid accumulation from 2,000 to 3,000 cubic centimeters to 500 to 600 cubic centimeters every 2 weeks. On the other hand, Desforges and associates have reported a series of 4 patients in whom the hepatic artery was ligated for portal hypertension. They noted no effect on ascites in 2 cases and had 1 death in a third patient due to massive hematemesis.

Madden has reported 8 patients who had hepatic and splenic arterial ligation for hepatic cirrhosis, 7 of whom had ascites. Four died in the immediate postoperative period and 3 of the surviving 4 died of hemorrhage, 3 weeks, 4 months, and 8 months postoperatively. Five patients had portal pressures taken before and after ligation. It was found that before ligation pressures ranged from 32.1 to 48.2 centimeters of water and after ligation from 29.8 to 42.1 centimeters. Taylor and Rosenbaum question the occurrence of a constant and effective decrease in portal pressure following hepatic arterial occlusion.

A cirrhotic liver already compromised as to its blood supply may be even more seriously affected by being deprived of the major part of its arterial circulation. Indeed, Keety and co-workers, by means of a three dimensional glass plate preparation, have shown that the regenerating liver nodule is supplied mainly by arterial blood, and that since the hepatic arterioles carry a high pressure head, the hepatic arterial circulation remains intact longer than the venous circulation in the seriously damaged liver.

It would seem then that depriving the damaged liver of its arterial supply is dangerous. Early enthusiasm for this method of treating patients with portal hypertension has apparently given way to a more skeptical opinion.

SUMMARY

An attempt has been made to prepare a laboratory animal with a true Laennec type cirrhosis and portal hypertension upon which hepatic arterial ligation could be carried out and evaluated. Dogs were prepared by weekly administration of carbon tetrachloride by stomach tube. Evidence of acceleration of the development of cirrhosis was obtained in a few dogs that had partial ligation of the thoracic inferior vena cava plus carbon tetrachloride administration. This proved too toxic and only 2 of 6 dogs so treated survived until the termination of the experiment.

The animals were followed by monthly liver biopsies. Seven of 23 dogs survived to develop advanced cirrhosis, and the hepatic and gastroduodenal arteries of these animals were doubly ligated and divided. Portal pressure readings were taken before and after the ligations and before sacrificing the surviving dogs 15 to 29 days later. The 2 dogs with the most advanced cirrhosis died of liver ischemia and gangrene 23 hours and 3½ days after arterial ligation was performed, despite large doses of penicillin. The 5 dogs surviving surgery all sustained decreases in portal pressure up to the time of sacrifice (ranging from 5.5 to 23 cm. of water). No significant pathologic changes were noted in the livers at the time of sacrifice when comparison was made to biopsies taken at time of arterial ligation.

The recent literature concerning therapeutic ligation of the hepatic artery and other celiac branches for portal hypertension is briefly reviewed. Most investigators seem to doubt the efficacy and safety of arterial ligation as the definitive treatment for bleeding esophageal varices or ascites caused by cirrhosis.

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THE EFFECT OF ACTH ON THE INTEGRITY OF ANASTOMOSES OF THE COLON

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THERE HAS BEEN considerable interest in the relationship of treatment with ACTH and cortisone to the healing of wounds since Ragan (8) first reported retarded wound healing in patients on ACTH therapy. The experimental studies done on this problem have yielded results that conflict in some respects. The investigations of Ragan (4), and Spain and others with granulating wounds in rabbits and mice indicate that ACTH retards the healing of wounds. However, recent experiments by Schilling and Taylor and their associates on skin wounds healing per primam in guinea pigs and rats, and by Cole and Muller and their co-workers on skin wounds and cardiovascular suture lines in dogs failed to demonstrate significant differences in the healing of wounds of control animals and those treated with ACTH and cortisone. A summary of these experiments including the dosages used, may be found in the paper of Muller and associates. The conflict in the experimental results may be attributable to the differences in the species of experimental animals, to the dosage of the hormone used, or to the particular type of wound or tissue studied. For example, Muller suggested that the factor of abundance of blood supply might explain the good healing of cardiovascular suture lines in the presence of cortisone which his experiments demonstrated.

The effect of ACTH and cortisone on anastomoses in the gastrointestinal tract is important for obvious reasons. Great caution has been advocated in the use of these agents in the presence of healing anastomoses by Hume and Moore. In the clinical series cited by Zimmerman, 4 of 10 patients with intestinal anastomoses treated with ACTH developed suture line leakage. Ragan (7) has stated that the depression of wound healing by ACTH is a function of the dosage, the larger doses inducing depression where lower doses do not. The purpose of this study was to determine the effect of varying doses of ACTH on end-to-end anastomoses of the colon performed with minimal soiling of the peritoneal cavity at the time of operation.

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METHOD

The experimental animals were healthy male mongrel dogs fed on ordinary kennel rations prior to surgery. Ten test animals and 10 control animals weighing from 6.4 to 18.9 kilograms were subjected to identical procedures following a 24 hour fast. Under ether-oxygen anesthesia the abdomen was entered through a left paramedian incision. The transverse colon was transected between the right colic and middle colic arteries without disturbing the marginal artery. The clamped cut ends of the colon were closed with Parker-Kerr basting stitches. By using fine silk on straight intestinal needles, the anastomosis was performed with a single row of Halsted stitches approximately 3 millimeters apart. After removal of the basting stitches the abdomen was closed in three layers. Postoperatively all animals were fed milk ad libitum immediately and for the 7 days before sacrifice.

After closure of the abdomen each animal in the test series was given an injection of 160 units of repository ACTH subcutaneously. A similar injection was given daily for 7 days. As the weight of the animals varied, the amount represented dosages of

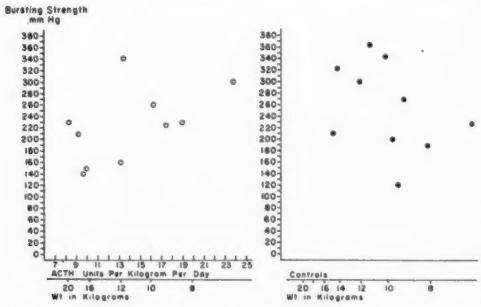

FIG. 1. Comparison of bursting strength values of anastomoses in animals treated with ACTH and in non-treated controls.

from about 8 to 23 units of ACTH per kilogram per day. No antibiotics were used. Samples of blood were drawn at intervals and examined for total protein, hemoglobin, and eosinophiles. The animals were observed daily for signs indicative of peritonitis from suture line leakage. On the seventh postoperative day each animal was killed with ether. After examination of the contents of the abdomen a 10 centimeter loop of colon containing the anastomosis was removed and tested for bursting strength by the Harvey method. With the ends of the loop closed the intraluminal pressure was increased at a rate of 10 millimeters of mercury per second by compressed air until the first bubbles of gas were seen escaping from the submerged specimen. The pressure at this instant and the site of the leak were noted. The anastomoses were fixed in formalin for microscopic examination. Hematoxylin and eosin stains were done on the sections.

RESULTS

The total protein and hemoglobin determinations revealed slight drops from preoperative values within a range of 1 gram per 100 cubic centimeters in both treated and control animals. The eosinophile counts of the animals given ACTH fell an average of 99 per cent on the first postoperative day and remained at this low level for the duration of the experiment. The eosinophile counts of the control animals showed a variable change from preoperative values, falling from 10 to 50 per cent, as has been noted by Coppinger and Godner in patients undergoing surgery.

No difference was noted in the postoperative course of the animals in either group. Suture line leakage was not induced with doses of ACTH as high as 23.4 units per kilogram per day. The bursting strength of the anastomoses in the control series ranged from 120 to 365 millimeters of mercury with a statistically significant mean value of 257 millimeters of mercury (t value = 11.40). The bursting strength of the anastomoses in the ACTH series ranged from 140 to 340 millimeters of mercury with a statistically significant mean value of 224 millimeters of mercury (t value = 10.98). The site of the first leak under pressure was always at the suture line. No correlation was evident between the dosage of ACTH and the anastomotic bursting strength. For example an animal receiving 23.4 units of ACTH per kilogram had an anastomotic bursting strength of 300 millimeters of mercury, while an animal receiving 10.6 units per kilogram per day had an anastomotic bursting strength of 150 millimeters of mercury (Fig. 1).

Examination of the hematoxylin and eosin stained sections of the anastomoses revealed well advanced fibroblastic proliferation and collagen formation without edema. Angioblastic proliferation and vascular ingrowth at the region of the suture lines were visible in all sections. Chronic inflammatory cell accumulations around the silk suture material were minimal. The microscopic appearance of both treated and control specimens was remarkably similar. There were no features by which the two series could be differentiated (Figs. 2 to 5).

DISCUSSION

In evaluating the results of the bursting strength determinations, the effect of the suture material present in the anastomoses must be considered. Fellows and associates demonstrated that the healing curves of intestinal anastomoses tested with and with-

Fig. 2.

Fig. 3.

FIG. 2. Section through anastomosis of animal which received 17.5 units of ACTH per kilogram per day. Note density of collagenous tissue and presence of new blood vessels. Hematoxylin and eosin, ×14.

FIG. 3. Section through anastomosis of nontreated control animal. Compare with Figure 2. Hematoxylin and eosin, ×14.

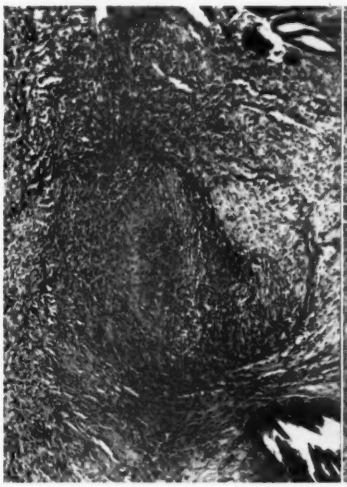

Fig. 4.

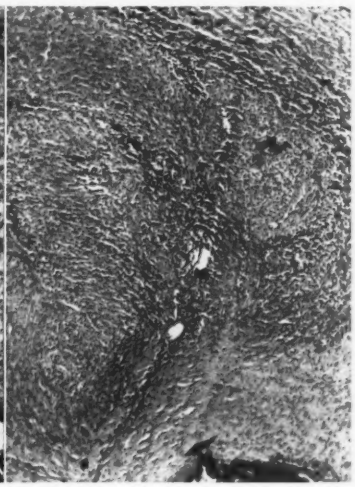

Fig. 5.

FIG. 4. Section of anastomosis of ACTH treated animal at higher power (×63). Silk suture in corner of section. Note numerous fibroblasts.

FIG. 5. High power view of anastomosis of nontreated control animal. Compare with Figure 4.

out suture support intersect at the seventh day. It would seem, therefore, that the silk sutures did not alter the end points in the bursting strength experiments. The bursting strength values found in these experiments correspond to those found in previous studies by Sako and Wangensteen on colon anastomoses in dogs.

Muller pointed out differences in the corticoid hormone dosage in various wound healing experiments and mentioned the difficulty of controlling the dosage in the dog with eosinophile counts because of their variability from animal to animal. We found the eosinophile count a valuable index of the action of ACTH. An almost total reduction in the number of circulating eosinophiles occurred with the doses of ACTH used. The ACTH dosage in these experiments is far in excess of clinical levels, the highest being equivalent to over 1,600 units per day in an adult patient.

It would seem significant that no demonstrable depression of healing by ACTH occurs in the anastomosis of the colon with the constant fecal contamination of the mucosal surface. This result is in agreement with surgical studies of per primam healing in other tissues in the presence of ACTH and cortisone. The factor of blood supply cited by Muller to account for the lack of influence of cortisone on healing of cardiovascular anastomoses is, of course, not at work here.

SUMMARY

Suture line leakage was not observed in a series of 10 dogs given large daily doses of ACTH following end-to-end anastomoses of the colon. The strength of the suture lines was not significantly altered by ACTH administration as compared with nontreated controls. The histologic characteristics of the anastomoses of treated and nontreated animals did not differ. No correlation was evident between the amount of ACTH given and the strength or appearance of the anastomoses.

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AMPUTATION AFTER SURGICAL SYMPATHECTOMY FOR OBLITERATIVE VASCULAR DISEASE

Incidence After 309 Sympathectomies

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TODAY, ONE of every six surgical papers is written on the treatment of vascular and cardiovascular diseases. Longevity, which has increased the life span from the average age of 47 years at the time of Abraham Lincoln to 77 years today, is one of the reasons. Two out of every 3 persons alive after their fortieth birthday will die of some cardiovascular disease or its complication (25). Before modern preventive medicine and surgery was practiced, most patients did not survive until the age when vascular lesions became of importance. Now, with excellent pediatric care, the control of contagion, the antibiotics, and the advances in anesthesia and surgical skill, patients live to a time when degenerative diseases, of which those of the vascular system are foremost, must be met and controlled if the patient is to survive. For example, 40 per cent of males at the age of 40 already have arteriosclerosis (15).

If the muscle, bone, or nerve supply to a part is injured the function of the part may be lost. If the blood supply is lost, the part or the individual is destroyed. These lesions challenge us for their solution whether or not vascular surgery is our primary surgical interest.

The sympathetic system plays a major role in the symptomatology, prognosis, and therapy of many lesions of blood vessels. Some diseases are *primarily* due to its overactivity. Raynaud's disease, causalgia, frostbite, and, to some extent, the postphlebitic syndrome develop from an overactivity and overstimulation of this system. Many of the lesions caused by these diseases can be relieved, or even reversed, in their disease process by an interruption of this sympathetic system.

In other diseases, the sympathetic system plays a *secondary* part. In these, the spastic and occlusive lesions which develop in the artery and its collaterals are of most importance. The vasoconstriction effect manifests itself extensively and sometimes dominantly on a reflex basis secondary to the stimulus of an occlusive arterial lesion. The occlusion itself may be precipitated or propagated by sympathetic overactivity. The purpose of the present article is to re-emphasize the part that the sympathetic system and sympathectomy may play in the course and therapy of the occlusive arterial lesions, the remaining unconquered killer of the largest number of patients with which we must contend today. We believe we can prove that, judicially applied, sympathectomy as a treatment is an important if not the most essential part of the therapy.

The surgeon's interest in a patient with obliterative arterial disease has progressed from the stage of amputation for gangrene. Gangrene today means that therapy was neglected, delayed, or that it failed.

The surgeon's potential part in the therapy of occlusive arterial lesions, particularly sympathectomy, is accepted by most but not all of our medical confreres. Many medical doubters who are sincere, honest, and intelligent internists deny that this operation has a part to play and believe that better results can be obtained without using

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that "last resort" surgery. This term, "last resort," has delayed the development of surgical therapy for these lesions. The surgeon often is called only when the lesion is advanced hopelessly. To overcome this feeling among the internists, we must show that the mortality and morbidity can be reduced by surgery, including sympathectomy.

THE SYMPATHETIC SYSTEM

The sympathetic system is still not well understood, although its anatomy and physiology have been known for a long time. Galen made the earliest reference to the sympathetic system in the second century, and Vesalius described both the sympathetic chain and its ganglia in 1543. In the sixteenth century, Harvey discussed the connection between the circulation and the sympathetic system, and Claude Bernard, in 1851, demonstrated that the sympathetic system controlled metabolism and body temperature. John Hunter first noted that the blood vessels contracted when subjected to trauma.

The sympathetic system primarily appears to be a defense mechanism in which a reflex vasoconstriction occurs in blood vessels in response to some stimulus such as trauma. This trauma may be a direct one, such as a gunshot wound or laceration, in which event nature attempts to prevent excess hemorrhage from the vessels by spasm. In addition, blood is forced out from the injured vessel and collateral vessels by this spasm so that these vessels are not full of clots and remain patent to carry blood again if their continuity is re-established. This trauma to initiate the spasm need not be an external one. Thus an arterial plaque, clot, or calcium deposit may release the stimulus to the reflex vasoconstriction.

The physiologic mechanism of this spasm still is not well understood. There is an autonomous spasm at the cell level as was shown by Landis (16) in the severed ears of a rabbit and repeated by Levinson and Essex and Page. Page produced spasm in the vessels of a rabbit ear by injecting a substance contained in the blood of a shocked dog's ear. This chemical which causes spasm has been called by various names. Bach, Gopfert, and Lewis named this substance histamine and White described it as sympathin. "Defibrinated blood" was the term applied to it by Landis (17), and Page and Chambers considered it some type of unknown toxin. To simplify the matter, our clinic has referred to this stimulator as "spastin."

There is also a nervous origin of vasoconstriction as has been demonstrated by Phemister and Barnes and Trueta. Whether this is a direct neuropathway, in which a reflex is set up by afferent stimuli from the source of the stimulus to the cord and ganglia and then by efferent stimuli to the vessel which goes into spasm, is not clear. It may be that a chemical is spilled into the blood by some reflex action which causes the subsequent constriction. The determination of whether this is neurogenic or chemogenic in origin is not of clinical significance. The important thing is to recognize the fact that spasm does occur in response to a stimulus. The degree of spasm varies with the stimulus and is not the same in different individuals. In general, it is dependent upon the type and degree of stimulus, the condition of the blood vessel and of the sympathetic system, and their ability to respond to the stimulus.

The deposit of a plaque or clot upon a vessel wall is sufficient trauma to initiate a spasm of the diseased vessel and collateral vessels in patients who have occlusive arterial disease. If this spasm is great, it may be sufficient in itself to slow the blood stream and permit clotting. This possibility increases with the narrowed lumen and the secondarily slowed blood stream. Thus, one can see that the disease, per se, may be the initiator and propagator of a reflex vicious cycle which can become self-perpetuating. The interruption of such a cycle before final clotting occurs is of therapeutic value. It is our belief that the best place to interrupt such a mechanism is at the ganglion itself. It has been demonstrated, to our satisfaction, that if this cycle is broken up before

permanent damage has occurred, the progression to occlusion may be retarded, may be segmented, or may even be reversed.

THE IMPORTANCE OF PERIPHERAL RESISTANCE

The part that peripheral resistance plays in the pathogenesis of occlusive arterial disease has not been emphasized sufficiently. For example, we know that in a normal individual with a blood pressure of approximately 120/60 millimeters of mercury the fall in the systolic pressure from the aorta to the terminal branches of the arteries is about 25 millimeters of mercury pressure (to 95 mm. Hg). When that blood reaches the capillary bed from the terminal arteries, the fall in pressure is 65 millimeters of mercury more (to 32 mm. Hg). It requires, therefore, 2½ times the pressure to overcome the resistance in the arteriolar bed as it did for the blood to pass from the aorta to the end of the main arteries. As Learmonth has pointed out, the arterioles have a cross-section of only 25 times more than the terminal artery branches, yet in resistance it takes 1,000 times greater pressure to overcome the arteriolar resistance than it did in the arterial branches. We believe that sympathectomy dilates the arterioles and releases their resistance.

CONSERVATIVE TREATMENT

The conservative treatment of occlusive arterial disease is quite well standardized. In essence, it consists of:

1. Keeping the skin covering or envelope intact. By this, it is meant that care is taken to prevent any skin breaks due to poor hygiene, trauma, thermal changes, fungus infection, and all other causes.

2. Stimulation of collateral circulation and efforts to dilate what remains of the original circulation. This can be done to some extent by use of the part below the fatigue stage, and by warm baths and postural changes.

3. The avoidance of all constricting or spastic elements, whether they be physical or chemical. In this respect, all tight-fitting garments, bandages, or shoes must be avoided; care must be taken that no casts or dressings restrict the circulation. The main chemical to be avoided is nicotine in the form of tobacco. No one doubts, any longer, the detrimental association of nicotine and arterial disease. Other chemicals to be avoided are the vasoconstrictors and those in the ergot family.

4. As the blood stream begins to slow down with the accumulation of the occlusive elements in the arteries, there is more tendency to thrombosis. As noted previously (23, 24, 28), anticoagulants, used correctly, will prevent a clot in a slowed stream as occurs in arteriosclerosis for a longer time than in those patients who do not have such properties in their blood.

SURGICAL THERAPY

Surgical treatment has been of the direct and indirect types. The blocks of the artery are frequently segmental and when so efforts are made to bridge or by-pass these blocks with grafts. This therapy has not been perfected as yet but is of great potential value. For this type of operation, an open vessel distal to the block is necessary.

Another direction of surgical efforts is to release the vasoconstriction by interrupting the sympathetic fibers which cause this constriction.

COLLATERAL CIRCULATION

In a segmental occlusion the patient must depend upon one of three types of collateral circulation or some substitute for the main vessel if the part is to survive. The collateral circulation can be subdivided into:

1. Hypervascularization vessels. These vessels are small and are either preformed or dilate or develop after the occlusion occurs.

2. Supplementary branches (Fig. 1). These are a hypertrophy of the small branch arteries in the muscles and particularly around the joints. The supplementary branches are partially effective in maintaining the circulation.

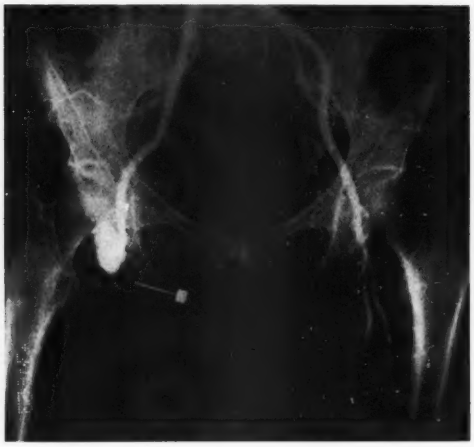

FIG. 1. Aortogram showing advanced arteriosclerosis. Femoral arteries obliterated left side with aneurysm formation on right side. Absence of distal patent major vessels makes reparative operation impossible. Treatment consists of extensive sympathectomy. Note collateral circulation.

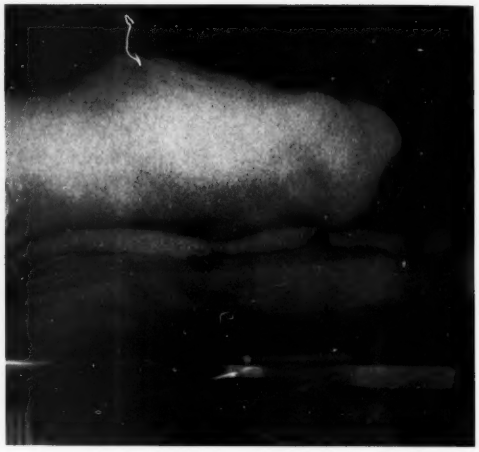

FIG. 2. Position for extraperitoneal lumbar sympathectomy. Patient on table with a lumbar break. Forty-five degree angle from the surgeon's side permits viscera to "fall away" from the surgeon. Arm on operation side extended above the head to increase the distance between the crest of the ilium and the costal margin.

3. Bridging collaterals. These "vital detours," as we call them, are larger and may attain sufficient size to permit complete function of an artery distal to the block. As pointed out previously (13, 14), all three types of collateral circulation are improved by surgical sympathectomy.

ANATOMY OF THE LUMBAR SYMPATHETIC SYSTEM

Since this discussion will be limited to the lumbar sympathetic chain, a word about the anatomy is of importance. This system primarily is a plexus and *not* a nerve. The anatomy of the lumbar sympathetics has been traced by many observers and more recently by Edwards, Ray, Kuntz and ourselves (25). The lumbar chain begins as a thin, string-like attachment from the twelfth thoracic. The sympathetic chain usually is lateral to the vertebra, but tightly attached to it, and often is crossed over by the lumbar veins at right angles. The ganglia vary in number and may fuse. They number from 3 to 4, but there may be as many as 8. Any thickening in the cord itself may be a ganglia. Each lumbar nerve has from 1 to 3 or 4 communicating branches, and these may anastomose widely with each other. They may arise at the level of the ganglia, but they also may arise between the ganglia. In general, the twelfth, first, and second lumbar rami ascend after their origin; the third usually goes transversely, but may ascend or descend; and the fourth and fifth usually descend in their course. Some of these rami will run in the psoas muscle itself. The external iliac and genitofemoral nerves also serve at times as carriers for sympathetic fibers and may account for the failure to get an adequate denervation when only the chain itself is removed.

While in the male the fourth lumbar spine anatomically is at the level of the iliac crest, in the female the fourth disc or fifth lumbar vertebra is at the level of the crest. In the usual position used in retroperitoneal sympathectomy, the promontory of the sacrum is elevated above the crest. Lumbar veins, periaortic lymph nodes, their nerves and blood vessels confuse the operative picture. An extra muscle origin of the crux of the

diaphragm from the vertebrae may cover the chain, as may other fascias and muscles in this area. Other nerves, blood vessels, lymph nodes, lumbar veins, and even the ureter may further obscure or mask the identification of the sympathetics.

TECHNIQUE OF SYMPATHECTOMY

From our experience, adequate sympathectomy effect cannot be obtained by the removal of the second and third ganglia alone, as is advocated in most operative techniques. Lumbar sympathectomy (Fig. 3), to be complete, should always include every lumbar ganglia, including the fifth lumbar if it exists, often the twelfth dorsal, and each nerve filament which makes up the plexus. We believe that often the poor or equivocal results reported by many clinics after sympathectomy are due to the fact that what they consider a sympathectomy is an entirely inadequate effacement of the sympathetic innervation. This opinion is further emphasized by the fact that we have reoperated and successfully removed ganglia from 19 patients in our series who had previously had a so-called sympathectomy with poor results.

ANESTHESIA

Lumbar sympathectomy in our hands is most safely performed under spinal anesthesia. We are certain that many of our older patients, subjected to sympathectomy safely, could not have withstood a general anesthesia. Collins of our Anesthesiology Department keeps the anesthesia level ideally low with a hypobaric technique. Whether a hyperbaric or hypobaric technique is used depends on the experience of the anesthesiologist. We feel strongly that this anesthesia should *not* be augmented by pentothal or other general anesthetics, which are too often given for the benefit of the anesthesiologist and not for the patient. We have shown in a series of 30 operations on patients over the age of 80 that this anesthesia is a safe one. Only 1 death occurred in this group (5, 6).

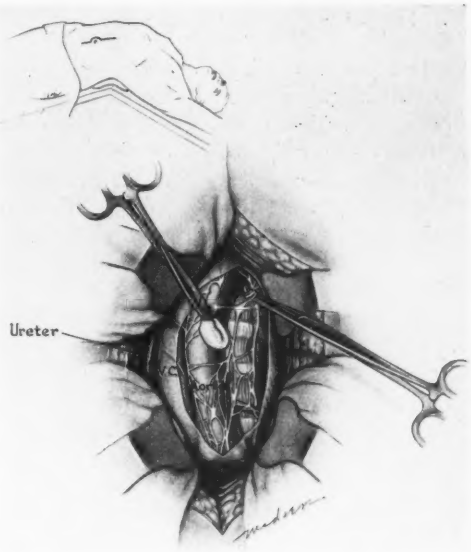

FIG. 3. Lumbar sympathectomy. Note anatomy of the sympathetic plexus. Each nerve component and ramus must be resected. Complete effacement constitutes satisfactory sympathectomy. Insert shows position for transperitoneal lumbar sympathectomy.

RESULTS OF SYMPATHECTOMY

Our clinic has used surgical sympathectomy widely in the treatment of occlusive arterial disease. It is used routinely prior to direct arterial surgery.

During a 5½ year period, from June 1948 to December 1953 inclusive, 504 surgical sympathectomies have been performed. These 504 operations were performed on 362 patients during this period. Three hundred and nine of these operations (61 per cent) were performed on 221 patients for occlusive arterial disease. The other diseases for which operations of this type were performed included: venous disease in 70 cases; Raynaud's and allied spasm in 29; causalgia in 16; and others (aneurysms and lymphedema) in 26.

These operations were performed on 236 males and 73 females, a ratio of 3 males to 1 female corresponding to the sex incidence of this disease. The average age of these patients was 58 years, the oldest being 87 and

the youngest 17. Thirty sympathectomies were performed for occlusive arterial disease on patients over 80 years of age.

Our analysis of these patients and their operative response has been made most critically. Often figures are made to confirm any fact an author believes. The two worst results obtainable in treating the patient with occlusive arterial disease are loss of life or loss of limb. There can be many extenuating circumstances contributing to both of these lamentable end results. Extensive and rapidly progressing disease, advanced age, severe cardiac, renal, or diabetic complications, the continuation of smoking, and further trauma as well as gangrene already present at the time of the sympathectomy, all may play an extensive part and can be used, if one desires, to vary his results and to prove a point. For example, in some of our patients sympathectomy was performed in an effort to amputate at a lower level than would otherwise have been possible. In this study, however, all such factors have been discounted and our figures were analyzed to show two things. Did the patient lose his life or did he lose his limb after a sympathectomy was performed? We have had a follow-up of from 6 months to 5 years on 210 of our 309 patients (64 per cent). Since death or loss of limb usually shortly follows operation if the procedure fails, we consider our findings representative.

DEATHS AFTER SYMPATHECTOMY

Of these patients, 9, or 3 per cent, who had a sympathectomy died. Seven of those 9 were over 60 years of age and 1 was over 80. Of these deaths, 5 died of coronary occlusion, 1 of progressive gangrene, 2 of generalized arteriosclerosis, and 1 of mesenteric thrombosis. The operation per se did not appear to contribute to their demise, but they died during the postoperative period and are included as operative deaths.

AMPUTATION AFTER SYMPATHECTOMY

Of the patients who had sympathectomy, 184 had arteriosclerosis without diabetes. There were 22 amputations in this group, or an amputation rate of 11 per cent. Ninety-one of the patients had arteriosclerosis and diabetes, and there were 31 amputations, or 34 per cent, required in this group. This figure again points up the importance of infection which is present in the diabetic so much more often than in those without diabetes in determining the outcome. There were 4 amputations after the 20 sympathectomies performed on patients with thromboangiitis obliterans. Thus there was a 20 per cent amputation rate in this group. In discussing extenuating circumstances we would say that only the 20 patients with the most advanced disease were operated upon. Our over-all picture of 1.6 per cent amputations for thromboangiitis obliterans in the 5½ year period, however, speaks well for the conservative management in this group. Of the 9 patients who had an acute arterial occlusion and had sympathectomy, there were 2 amputations, giving a figure of 22 per cent. Three of the 5 patients with frostbite who had sympathectomy came to partial amputation, and in this group we have an amputation rate of 60 per cent. Thus we have a total amputation rate of 62 after 309 sympathectomies, or 20 per cent. Twenty-four (39 per cent) of these amputations were below the knee, 35 (56 per cent) were above the knee, and 3 (5 per cent) were of a part of the foot. We believe that sympathectomy contributed to the lower operative site in the 39 per cent who had amputations below the knee.

SYMPTOMS AND AMPUTATION AFTER SYMPATHECTOMY

We compared the presenting symptoms of these patients with the amputation rate. The largest number of our patients (179) were operated upon for coldness and claudication of an advanced type. Only 8, or 4.4 per cent, of those came to amputation. Where there was ulceration and infection, as there was in 65 patients, 21, or 32 per cent, required amputation. Where there was actual gangrene, as was present in 35 pa-

tients, 23 amputations or 69 per cent were necessary. It is significant that of those patients who had pain at rest (16), half of them lost their limbs. Thus when there was gangrene or ulceration and infection, as occurred in 100 of our patients, 44 per cent lost their limb, but 56 per cent did not. Gangrene, pain at rest, and ulceration were the most serious symptoms prognostically, and in this series they occurred in that order. Sympathectomy was performed in the presence of other symptoms in 13 cases, in 2 of which (15 per cent) amputation was necessary.

In an effort to explain some of our failures to achieve good results, we analyzed the pathologic reports on these 309 sympathectomies. At operation time we all try to remove the tissue that needs to be removed, whether it be an appendix, a cancer of the stomach, or the sympathetic chain. All hospitals make an effort not to lose the specimens, to make the sections of the right tissue, and to report on these sections accurately. In 258 of the 309 operations, the presence of sympathetic chains, ganglia, or sympathetic nerves was noted on the pathologic report. In 17 of our patients, however, lymphoid tissue was reported; in 1, no nerve or ganglion was seen; and in 33 no pathologic report was found to have been returned, the specimen either having been discarded or the report lost. Thus, in 17 per cent of our patients we had no pathologic confirmation that lumbar sympathectomy actually was performed. Were other hospitals not in a similar status as far as their pathologic confirmation of the tissue removed, we probably would hesitate to present these figures. Nine of our amputations occurred in this group of patients—not a significant figure, however.

CONCLUSIONS

Sympathectomy, we believe, is an excellent ancillary therapeutic measure to employ in patients with occlusive arterial disease, provided that (1) gangrene is not already present; (2) it is not used to replace the underlying medical management; (3) the patient has a fair chance of surviving the operation; (4) the patient has given evidence of a desire and ability to stop smoking; (5) all other corrective measures for the underlying disease are taken. Our series of patients demonstrated that in 247 of 309 sympathectomies (80 per cent), amputation did not follow sympathetic denervation, and these were in patients with advanced occlusions. The sympathetic denervation must be a complete effacement, not a mere partial resection.

It is the belief in our clinic that many poor results are due to an ineffective or inadequate sympathectomy. Sympathectomy is not a cure-all, such as an appendectomy or cholecystectomy; but when carefully employed, it may be sufficient to maintain the delicate balance between the vascular supply, infection, and loss of limb. Pain at rest is a dangerous symptom. In the patients with active gangrene, amputation will follow 2 out of 3 times in spite of, and not because of, sympathectomy. Paradoxical gangrene per se has not been seen by the author. It is his feeling that if gangrene occurs after sympathectomy it is because the disease was already irreversible or operative trauma caused an occlusion.

When the symptoms are those of claudication and coldness, 95 per cent of the patients will keep their limb after sympathectomy. If there are open lesions, 2 out of 3 will not require an amputation. Even when gangrene is present, 5 to 6 of every 10 will not lose their legs after sympathectomy. It is admitted that the disease is progressive and some patients may later lose their legs. Sympathectomy, however, is a safe and often successful treatment for these patients.

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ACUTE UPPER ALIMENTARY TRACT ULCERATION AND HEMORRHAGE FOLLOWING NEUROSURGICAL OPERATIONS

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The attempt to find a reasonable explanation for the acute perforative lesions affecting oesophagus, stomach, and duodenum, which in three instances caused early fatality after operations for cerebellar tumor, has led, not only to a review of the extensive literature on the neurogenic aspects of ulcer pathogenesis, but also to certain experimental observations that strongly suggest the presence in the diencephalon of a parasympathetic center.—*Harvey Cushing*

THE APPARENT INCREASE in frequency and the gravity of acute alimentary tract ulceration and hemorrhage in the postneurosurgical period are problems which have received renewed interest and attention since the above report of Harvey Cushing in 1932. Lesions of the central nervous system, and in particular the hypothalamic area, have been held accountable in the past for the occurrence of this gastrointestinal complication. More recently, however, considerable doubt has been expressed concerning the specificity of the hypothalamus, or in fact any well localized anatomic region, in being solely responsible for the incidence of these alimentary tract changes. In view of recent reports which correlate clinical and experimental lesions of the diencephalon by French and associates and the role which adrenal corticosteroids may play in the pathogenesis of these upper gastrointestinal tract changes by Gray and his associates, a study of a large series of neurosurgical patients was made to determine the incidence, natural history, and possible mechanisms involved in these complications. Although various types of central nervous system and gastrointestinal tract disease may occur coincidentally, this investigation concerns only those patients who were subjected to surgery. In addition to the clinical presentation, the experimental findings in a group of 15 cats with stereotactically oriented hypothalamic lesions will be discussed.

An analysis of 7,000 operative and clinical records distributed over the past 30 years revealed 48 examples of acute upper gastrointestinal ulceration or hemorrhage during the postneurosurgical period, an incidence of 0.7 per cent. In a series of 943 craniotomies, there were 24 instances in which this complication occurred; in 350 suboccipital craniectomies it was found during the postoperative course of 7 patients. A careful inventory of gastrointestinal tract symptoms was made in all patients prior to surgery, and in 8 cases there were pre-existing complaints of varying severity. These same 8 patients had acute fatal, or nearly fatal, episodes of hematemesis following the neurosurgical operation. There were 12 patients who initially had a smooth postoperative course and who would have recovered well from the effects of the neurosurgical procedure had it not been for unexpected, sudden, and massive gastrointestinal tract hemorrhage, which was considered to have led directly to their death. In a total of 30 deaths from various causes in this series, 24 autopsies were performed, and in 15 instances an ulceration was present, or the cause of the gastrointestinal hemorrhage was determined. There were 9 examples of

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TABLE I.—CORRELATION BETWEEN ANATOMIC LOCATION OF NERVOUS SYSTEM PATHOLOGY AND SEVERITY OF GASTROINTESTINAL TRACT HEMATEMESIS

Location in nervous system	*—Gastrointestinal symptomatology—* *Severe hematemesis*	*Moderate hematemesis*	*Minor hematemesis*	*No. hematemesis*	*Total*
Frontal lobe	5	2	3	1	11
Multiple sites involved	3	1	4	1	9
Posterior fossa	4	1	2	—	7
Diencephalon	2	1	—	—	3
Temporal lobe	—	1	1	1	3
Parietal lobe	2	—	1	—	3
Cervical spinal cord	2	—	—	—	2
Thoracic spinal cord	—	1	—	—	1
Cervical vertebral column	1	—	—	—	1
Thoracic vertebral column	1	—	—	—	1
Lumbar vertebral column	3	—	—	—	3
Cervical sympathetics	1	—	—	—	1
Thoracolumbar sympathetics	—	—	1	—	1
Orbit	—	—	1	—	1
Paratrigeminal area	—	1	—	—	1
Total	24	8	13	3	48

single or multiple ulcerations at the cardioesophageal junction, stomach, or duodenum, which were the most common types of pathologic changes. The ulcerations extended through the muscularis mucosae of the involved structure and were grossly and microscopically characterized by lack of fibrosis and induration. There was a single example in which fatal hemorrhage was caused by rupture of esophageal varices; in 2 other patients, esophageal varices were important associated pathologic conditions. In the remaining 5 cases, there were multiple areas of mucosal erosion of the stomach and esophagus, which showed no evidence of penetration of the muscularis mucosae. None of these gastrointestinal changes could be confused with postmortem autolysis, and the mucosal erosions were similar to those described by Rokitansky in 1841 and almost a century later by Cushing. In the remaining 9 autopsies, no gastrointestinal tract disease was demonstrated, although hematemesis was a prominent feature in the postoperative course. However, careful gross and microscopic examinations of the gastrointestinal tract were not done in these 9 patients. There were 18 other patients who survived episodes of hematemesis, and subsequently made a good recovery. In one-third of the group who survived these complications, the bout of hematemesis was alarmingly severe, and in the remaining two-thirds, there were one or two episodes of coffee-ground vomitus without further evidence of hemorrhage.

Pathologic processes in the nervous system were all verified by autopsy, frozen section, or by detailed surgical descriptions in such instances as arachnoidal or osteoarthritic changes, which produced neurologic symptoms. Intracranial pathologic change was present in 36 patients and the most frequent tumor type encountered was the glioblastoma multiforme. Cerebral metastases, meningiomas, astrocytomas, and acoustic neurinomas followed in that order of occurrence. In 1 instance a suboccipital craniectomy was performed and although no pathologic condition was found, the patient succumbed to a massive gastrointestinal tract hemorrhage. There were 10 patients in a miscellaneous category in which the central nervous system was not involved by a pathologic process. The anatomic distribution of disease of the nervous system is tabulated in Table I, which shows a predominant involvement of the frontal lobe, then of the posterior fossa. A correlation of the anatomic position of the lesion in the nervous system with the upper alimentary tract hemorrhage or ulceration in the 12 patients in whom death was directly attributable to these complications revealed: 3 patients with frontal lobe glioblastomas; acoustic neurinoma in 2 cases; pituitary adenoma in 2 cases; frontal lobe metastatic carcinoma from the lung, posterior fossa metastatic renal carcinoma, cervical spinal cord arachnoiditis, and a diagnosis of no cerebellar pathology each in 1 patient. It may be concluded, from various reports in the literature and from our data, that the microscopic diagnosis of the tumor type cannot be correlated with the occurrence of the gastrointestinal tract hemorrhage or ulceration. It is significant that, in this series of 48 patients, disease of the cerebral hemispheres, and in particular the frontal lobe, was of more frequent occurrence than in-

volvement of the diencephalon or the posterior fossa. It is not probable that any extensive lesion would impinge in the hypothalamic-frontal pathways without also destroying other fiber tracts, so that it is doubtful that this factor is solely responsible for producing an autonomic imbalance as suggested by French.

CLINICAL OBSERVATIONS

Clinically, fatal hematemesis and ulceration usually occurred during the first 48 hours postoperatively, although there were several instances in which symptoms developed at a later period of 6 to 8 days, with subsequent death. The patients who survived the more severe bouts of gastrointestinal tract hemorrhage, and those who succumbed as a result of it, all demonstrated a state of marked shock, anemia, and hyperthermia. Minor episodes of hematemesis often occurred in the first 24 hours after surgery and generally did not recur, but any hematemesis was considered to be a grave prognostic sign because there was no accurate method of determining whether these episodes might continue with subsequent blood loss, shock, and death. Since the gastrointestinal tract history was completely negative in 83 per cent of the patients, the onset of hematemesis was seldom anticipated, and consequently prophylactic treatment could not be instituted. Treatment was conservative in all instances, and autonomic blocking agents and ulcer feedings were instituted; in no instance was an abdominal operative procedure carried out as a measure of treatment. The case mortality of the series was 25 per cent.

The majority of the coffee-ground vomitus was tested for the presence of blood, but usually the gastric emesis was of such color, volume, and consistency that its source could not be mistaken. The occurrence at autopsy of large amounts of blood in the stomach frequently confirmed the clinical progress notes. In 16 patients endotracheal ether was administered during the neurosurgical procedure, and the question of postoperative vomiting of previously swallowed blood from the nasopharynx might be raised. Repeated careful examination of the nasopharynx, or posterior nares, for clots of old blood ruled out hemorrhage from this extragastric location. All examples of "blood tinged" or "blood streaked" vomitus were excluded from the series, as well as the instances in which a definite nasopharyngeal bleeding point was identified.

There was radiologic evidence of duodenal ulcer in 2 patients prior to the neurosurgical operation, and 1 instance of diaphragmatic hernia; all had severe postoperative gastrointestinal tract hemorrhage. Duodenal ulcer was demonstrated in 1 patient and irregularity of the duodenal bulb in another after the neurosurgical procedure and a precarious recovery.

The clinical course and the pathologic findings which occurred in this series are illustrated by the following case summaries. The abrupt onset of hematemesis in the patient too ill to complain, with unrelenting gastrointestinal bleeding, shock, hyperthermia, and exodus were the progressive steps in these complications of the gastrointestinal tract.

In Case 1, the intracranial disease was extensive, the diencephalon was not involved, and the gastrointestinal tract pathology was proved grossly and microscopically to be an acute, recent process and not a chronic type of ulcer.

CASE REPORTS

CASE 1. The patient was a 57 year old white male who entered the hospital aphasic, with a right hemiparesis and papilledema. A large left frontal-parietal osteoplastic craniotomy was performed under novocain and avertin anesthesia. Cortical incision in the medial and inferior frontal gyri and the midtemporal area revealed a cystic cavity. Approximately 12 cubic centimeters of yellow fluid containing crystals were removed. An extensive resection of the lesion was not performed, but the patient was provided with a large decompression.

The postoperative progress was satisfactory for 12 hours, when he had a bout of hematemesis; the blood pressure became imperceptible. Blood was administered. Hematemesis continued and large amounts of coffee-ground material were removed by gastric suc-

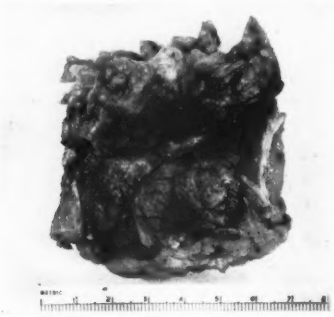

FIG. 1. Specimen of the duodenum showing a large perforated ulcer.

tion. The patient subsequently expired in marked shock, with anemia, and hyperthermia.

Autopsy revealed an anterior duodenal ulcer 1.0 centimeter in diameter which had perforated (Fig. 1). There was remarkable lack of gross induration about the perforation. Histologic sections through this acute duodenal ulcer showed minimal cellular infiltration by lymphocytes or polymorphonuclear leucocytes in the region where there was maximum destruction of the duodenal wall.

The third ventricle was not enlarged and there was no evidence of tumor in the region of the pituitary or hypothalamic areas. The frontal, temporal, and occipital lobes were occupied by a large cystic cavity measuring 6 to 7 centimeters in length (Fig. 2). Microscopically, the tumor was a metastatic carcinoma which had its primary site in the lung. Repeated questioning of the family revealed no previous history of gastrointestinal tract complaints.

Case 2 is an example of a patient who sustained trauma to the head, then had a neurosurgical diagnostic procedure, and subsequently had several bouts of hematemesis before death.

FIG. 2. The large cystic tumor cavity extended from the frontal into the occipital lobe.

CASE 2. The patient was a 58 year old white female who was comatose on admission; she was jaundiced, and there was a long history of alcoholism, but no definite history of craniocerebral trauma as related by the family physician. A ventriculogram revealed a right space-occupying lesion. There were no previous gastrointestinal tract symptoms. During the 5 to 12 hour period following the ventriculogram, there were several episodes of hematemesis. The patient expired before a more definitive operative procedure was performed.

Autopsy revealed a considerable number of dilated esophageal veins. At the junction of the posterior portion of the esophagus and the stomach, there was a large necrotic perforation measuring 1.0 centimeter in diameter with a black-gray necrotic base; there was no communication with the lower lobe of the left lung (Fig. 3).

In the right parietal-temporal-frontal subdural space there was a bluish fluctuant mass, which on opening the dura was composed of an estimated 150 cubic centimeters of nonadherent, nonorganized "currant-jelly" clot. The cranial vault was completely devoid of evidence of trauma or fracture. Section through the brain stem shows glial destruction and hemorrhage.

These gastrointestinal tract complications have been frequently encountered following suboccipital operations for posterior fossa lesions. Such was the situation in Case 3 of a patient who had a benign posterior fossa tumor and a vague preoperative history of epigastric distress.

CASE 3. The patient was a 50 year old white male who presented the signs and symptoms of a left acoustic neurinoma. For 1 year prior to admission he complained of moderate, burning, substernal and epigastric pain following meals, which was relieved by a bland diet. Preoperatively, this fact seemed to warrant no further investigation or treatment. A suboccipital craniectomy was performed under endotracheal ether anesthesia, and a partial intracapsular removal of a left acoustic neurinoma was performed.

Approximately 11½ hours postoperatively the patient began having numerous episodes of hematemesis. A Levin tube was passed and gastric suction was begun; atropine and amphojel were given. Large blood clots continued to be vomited and blood was obtained by suction. The patient expired 35 hours postoperatively in marked shock.

Autopsy revealed decomposed blood in the stomach and 4 ulcers, each approximately 1.0 centimeter in diameter which had shaggy edges, in the cardiac re-

FIG. 3. Photomicrograph of the large necrotic perforation of the gastric ulcer which shows the necrotic borders.

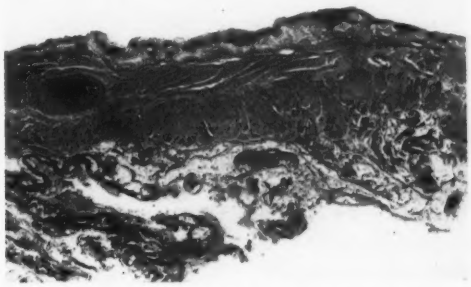

FIG. 4. Photomicrograph which shows acute ulceration in the cardiac region of the stomach along the lesser curvature. Similar ulcers were present in the pylorus.

gion along the lesser curvature; similar ulcers were present in the pylorus (Fig. 4).

There was a tumor mass lying to the left of the pons and medulla displacing them far to the right and indenting them deeply, so that one-half of the pons appeared to be missing. The tumor mass measured 4.5 centimeters in diameter (Fig. 5). There was a marked herniation cone at the level of the foramen magnum. The microscopic sections were typical of an acoustic neurinoma.

EXPERIMENTAL FINDINGS

Small destructive hypothalamic lesions were made in a group of 15 cats using the Clarke stereotaxic apparatus. Nembutal anesthesia was used intravenously (30 mgm. per kgm.), and a small area of bone was removed from the vertex of the skull. Without incising the dura mater, the monopolar electrode was introduced at the desired level with the apparatus firmly attached to the skull. The animals were autopsied at varying intervals from 6 weeks to 6 months; the brains were examined by serial sections through the hypothalamus for verification of the lesions. There were 5 animals with anterior hypothalamic lesions; 5 cats with tuberous lesions; and another 5 with posterior hypothalamic lesions. The lesions were bilateral in location and discrete in their extent. Autopsy examination of the entire gastrointestinal tract failed to reveal any evidence of either an acute or a chronic type of ulceration. There were no instances in which hematemesis or melena occurred in any of these animals. There were no mucosal erosions encountered, which might even be remotely analogous to the clinical lesions observed. These experiments supported the results of Martin and Schnedorf obtained in 1938 in our laboratory after similar, accurately placed stereotaxic electrolytic lesions in the hypothalamus.

DISCUSSION

There would appear to be no significant correlation between the specific disease process of the central nervous system and the

FIG. 5. Photograph of the left acoustic neurinoma.

production of gastrointestinal tract ulcer and hemorrhage. Infection, trauma, intoxications, cerebrovascular accidents, congenital deformities, intracranial tumors, and neurosurgical diagnostic procedures have all been reported in the literature to be accompanied by ulcerations and hemorrhages of the alimentary tract.

A review of the pathology in the nervous system in this series of 48 patients has substantiated these previous reports. In fact, examples of severe hematemesis occurred in the absence of any intracranial disease and following neurosurgical procedures in which the central nervous system was in no way anatomically involved at the time of surgery. Discrete, isolated intracranial lesions were infrequent; the hypothalamus and diencephalic areas were involved by pathologic change in only 4 patients, and in those instances the lesions were large expanding tumors of the pituitary. The conclusion reached by Globus and Ralston, that the hypothalamus was not necessarily an area of predilection for the formation of upper alimentary tract ulceration and hemorrhage is thus supported.

The results of Beattie, Keller, and Mogilnitzky, who found that gastrointestinal tract lesions followed diencephalic lesions in experimental animals, must be interpreted with some skepticism in view of the technical procedures employed. Hypothalamic lesions were made blindly either by transection of the corpus callosum or elevation of the temporal lobe, with suction in the region of the third ventricle, or by using hooks or probes. The resulting lesions were obviously neither specific nor discrete. There was frequently bleeding into the ventricular system and often careful histologic examination of the diencephalic area was not reported.

Recently, French and his associates have observed a group of patients with similar severe postneurosurgical hematemesis and gastrointestinal tract ulceration. In addition, they presented experimental data in which carefully oriented stereotactically hypothalamic lesions were placed with the Clarke apparatus. A group of 13 cats was used and ulceration and/or hemorrhage occurred in all but 1 animal. They concluded that lesions which involved the hypothalamus, or its afferent or efferent pathways, predisposed the patient to gastrointestinal tract disease, which in turn was precipitated by the stress of the illness and the trauma of surgery.

Interruption by a disease process of the frontal lobe connections of the hypothalamus itself or projections from this structure in the posterior fossa are not essential for the production of these gastrointestinal complications as is convincingly shown by 7 patients in this series in which the surgical procedure was neither intracranial in location, nor was the central nervous system exposed at any time. Since the cerebral pathologic conditions in the group of patients presented by French as well as in our group of patients were anatomically extensive, multiple pathways and cerebral centers were involved so that the physiologic effect of an isolated lesion was never obtained. McDonnell and McCloskey have reported that in autopsy material peptic ulcer occurred as a complication of general surgical procedures with a somewhat greater frequency than following neurosurgical operations and disease. Herbut made a similar report from the same laboratory in 1945.

It is rather difficult to reconcile the complete absence of gastrointestinal tract disease after discrete hypothalamic lesions in the cats recently experimented upon and in the larger number of monkeys and cats similarly studied by Martin and Schnedorf in our laboratory, and those changes encountered by French and his associates. The resolution of the differences becomes even more difficult when they report that perforations follow posterior hypothalamic lesions and hemorrhage occurs only after anterior hypothalamic lesions in experimental animals. Photomicrographs of the hypothalamic lesions were not included in their report, and although it is difficult to interpret accurately from the sketches of this area, the relative

extent of the destructive lesion would appear to be much larger. It may be added that French and his workers sacrificed their experimental animals before, or at the end of a 3 week period, whereas the cats in this series were carefully followed for a period of 6 weeks to 6 months. If superficial gastric erosions, comparable to the ones which French encountered, had been present in our animals, they would have healed before autopsy examination.

Gray and his associates have shown that the administration of adrenocorticotrophic hormone, cortisone, and the physical stress of surgery increase the secretion of gastric hydrochloric acid and pepsin in humans. A prolonged neurosurgical procedure may trigger the hypothalamus to stimulate the anterior pituitary to produce ACTH which activates the adrenal cortex to produce adrenal corticoids which directly stimulate the parietal cells and peptic glands. The precise physicochemical mode of action by which adrenocorticotrophic hormone and cortisone produce this increase in gastric secretion has not yet been shown, but such a response does occur in the presence of the intact or severed vagus nerve. All 8 patients in this series, with a previous history of gastrointestinal symptomatology, experienced a definite reactivation of symptoms and frequently disastrous episodes of hematemesis occurred after surgery. The stress mechanism(operation)and the adrenergic-corticoid phase which occupies the first 3 to 4 postoperative days would be comparable to the actual administration of large dosages of adrenocorticotrophic hormone or cortisone. Dragstedt has demonstrated in a limited number of patients a marked increase in volume of gastric secretion and total and free hydrochloric acid in the postcraniotomy state.

The patient's metabolic response to stress seems to be the most plausible explanation for the acute gastrointestinal tract hemorrhages and ulcerations which follow the stress of a surgical operation, in which the central nervous system may or may not be involved by a pathologic process, and in which the hypothalamus is rather infrequently involved. It would seem that acute upper alimentary tract ulceration and hemorrhage may represent extreme pathophysiologic responses to the stress of a surgical procedure. It is doubtful that a lesion of the hypothalamus is a necessary requisite for their occurrence. That the hypothalamus is concerned in the pituitary adrenal cortex balance is probable and this influence may be affected by different modes of stimulation.

SUMMARY

1. Upper gastrointestinal tract hemorrhage and ulceration following neurosurgical procedures are frequently highly fatal surgical complications. The gastrointestinal tract changes are acute in their pathologic characteristics.

2. There would appear to be no correlation between the histologic character of the pathology of the nervous system and the occurrence of the lesions of the gastrointestinal tract.

3. The anatomic extent of the pathology of the central nervous system in this series of patients was large, with most frequent involvement of the frontal lobe. Single pathways and cerebral centers were never selectively destroyed by the disease.

4. Central nervous system pathology was not a requisite for these gastrointestinal tract complications, since they were encountered following such procedures as laminectomy, hemilaminectomy, and trigeminal neurectomy.

5. There was reactivation of gastrointestinal disease in patients with previous history of complaints.

6. In a group of 15 cats, there was no gastrointestinal tract pathology following discrete anterior and posterior hypothalamic destructive lesions made by the Clarke apparatus.

7. It is suggested that these gastrointestinal tract ulcerations and hemorrhages represent an extreme pathophysiologic re-

sponse to the physical stress of surgery wherever its location.

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EVALUATION OF THREE METHODS OF URETEROCOLOSTOMY

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URETEROINTESTINAL ANASTOMOSIS is an exacting procedure which, to be successful, demands: (1) intestinal antisepsis, (2) fine operative technique and suture material, and (3) consideration for primary wound healing at the stoma. Validity of the third tenet becomes apparent in the following. Two methods of ureterocolostomy have been put forward recently, both from distinguished medical centers but diametrically opposed as to intricacy of technique. The Mathison procedure is designed to prevent reflux but also to avoid ureteral obstruction. It is essentially an end-to-side anastomosis of ureter to colon with interrupted sutures in which, in addition, a cuff of the adjacent colon envelops the distal extremity of the ureter and thus presumably provides a sphincter. The procedure of Kerr and Colby is intended for speed and simplicity. In this procedure the ureter is introduced into the bowel through a suitable stab incision and sutured to the serosa of the bowel without torsion or tension. The present work is an attempt to evaluate these techniques, emphasizing gross and microscopic changes at the distal end of the ureter. We shall also report on another method which we use clinically, namely, full thickness end-to-side ureterosigmoidostomy.

METHODS

The dogs varied in weight between 7.3 and 16 kilograms and were quarantined for at least 2 weeks. They were given 1 gram of streptomycin and terramycin daily with their food for about 6 days preoperatively. They were allowed only water during the last preoperative day. On the morning of surgery blood was drawn for serum urea, creatinine, sodium, potassium, chloride, and bicarbonate. Under sodium pentobarbital anesthesia (ca. 30 mgm. per kgm., i.v.) the abdomen was entered through the lower third of the linea alba. The lower colon was massaged cephalad for several centimeters at which level it was gently occluded with a moistened ligature of gauze to prevent upper colonic contents from contaminating the peritoneal cavity during ureterocolic anastomosis. The canine colon has no taenia but, rather, a well developed complete layer of longitudinal muscle and is relatively short without "sigmoid" or distinct rectum. The anastomoses were performed at the lower portion of the colon at about the level of the dome of the empty bladder. The ureters were divided close to the bladder and the latter easily removed after dividing and ligating the intraperitoneal urethra.

Three types of ureterocolostomy have been studied, which have been designated as I, II, and III. Type I has been described in detail by Mathison. His technique was followed closely. The sutures were No. 5–0 chromic catgut swaged to a fine curved needle without cutting edge. Type II is the classic simple pull-through ureterocolostomy with anchor suture, recently reproposed by Kerr and Colby. Type III is full thickness, end-to-side ureterosigmoidostomy somewhat modified from Chaput and Cordonnier (6, 7). In all types, ureteral blood supply was conserved and distal ureter mobilized only essentially. In the dogs, 1 gram of streptomycin was dusted into the paracolic gutters after completion of anastomosis. In type III, the terminal end of the ureter was cut into an ellipse

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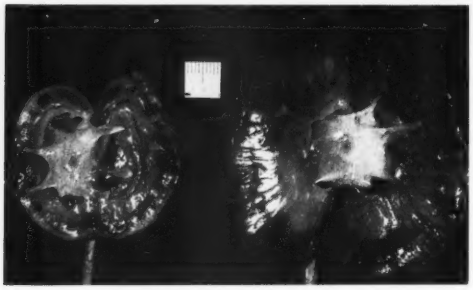

FIG. 1. Kidneys of dog A-1; sacrificed on one hundred and fiftieth postoperative day. Right kidney is small and hydronephrotic with markedly narrowed cortex; left kidney is moderately hypertrophied and scarred.

such that the long diameter was double the short diameter and the circumference of the ellipse could be apposed to the bowel without torsion or tension of ureter. A pair of guide sutures was passed through the full thickness of the ureter and of the bowel, about 1 millimeter from the cut surfaces, at the antipodes of the ellipse. The remaining sutures were set 1 millimeter apart between the guide sutures and interrupted. They were passed through the full thickness of wall of ureter and of bowel about 1 millimeter from the cut surfaces.

In the patients, bowel antisepsis was as follows: Beginning on the fifth preoperative day, 0.5 gram of streptomycin was given twice daily orally and 50 milligrams of polymyxin thrice daily orally; the diet was soft, and a soapsuds enema was given daily. During the preoperative 24 hours the patients received only clear fluid orally. On the morning of surgery soapsuds enemas were given until the returns were clear. A swab from the lumen of the sigmoid, taken at surgery, cultured only alpha streptococcus or micrococcus. Nasogastric suction and exclusively parenteral feeding were maintained for 5 to 7 days postoperatively to reduce the rate of bacterial growth in the colon.

In the dogs, no drain or rectal tube was used; 300,000 units of procaine penicillin were given immediately postoperatively and once again on the first postoperative day. Ample liquid with fecal suspension was ejected per rectum within the first postoperative day by all animals. Several of the dogs developed a poor appetite and had to be sustained on fresh ground beef and milk. Occasionally Ringer's solution, with or without dextrose, was given subcutaneously. On the whole, appetites improved in capacious outdoor cages. Loss of skin turgor could hardly be ascribed to an abnormally high output of electrolyte, as indicated by the following 24 hour fasting water and electrolyte losses per rectum: Dog A-1, 10 kilograms, on the one hundred twelfth postoperative day lost 1,910 cubic centimeters of feces plus urine containing a total of 22.7 milliequivalents of sodium ion, 72 milliequivalents of potassium ion, and 17 milliequivalents of chloride ion, or an amount

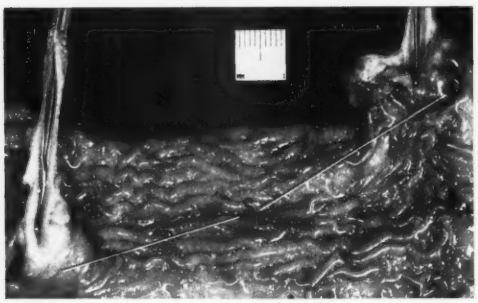

FIG. 2. Ureterocolostomy in dog A-1; ureters slit longitudinally; both ureters moderately dilated. Note rosette or bud around each ureteral stoma, *S*, causing stenosis.

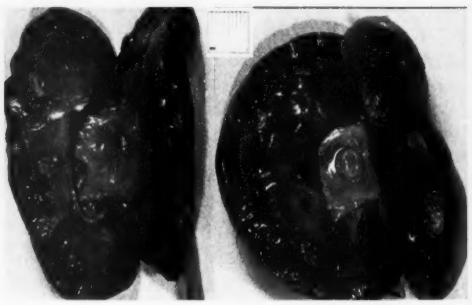

FIG. 3. Kidneys of dog A-2; thirty-third postoperative day. Right kidney is moderately hydronephrotic and scarred. Left kidney is somewhat hypertrophied and slightly hydronephrotic but not grossly infected.

of chloride ion present in about 165 cubic centimeters of extracellular fluid. Dog A-12, 10 kilograms, on the fiftieth postoperative day lost 560 cubic centimeters of feces plus urine, containing 16.2 milliequivalents of sodium ion, 10.6 milliequivalents of potassium ion, and 7.9 milliequivalents of chloride ion, or an amount of chloride ion present in 76 cubic centimeters of extracellular fluid.

Loss in extracellular fluid was thus apparently due to deficient intake associated with hydronephrosis, pyelonephritis, and acidosis—all of which generally were present. Even grade 1 hydronephrosis (as in dog A-1) apparently was responsible for reduced appetite. That loss of skin turgor was due largely to deficient intake was evident from the few dogs which did not lose their appetites and maintained their weight and normal skin turgor.

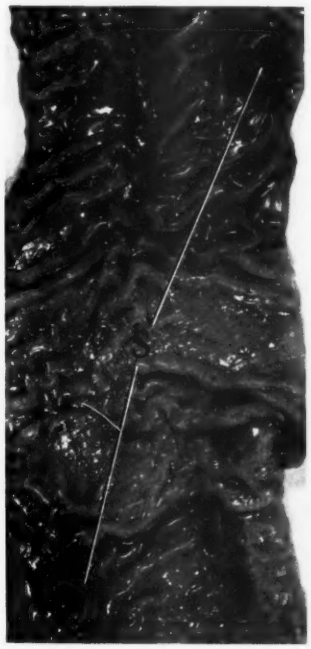

FIG. 4. Ureterocolostomy in dog A-2. Ureters are slightly dilated. Note rosette at each ureteral stoma, *S*, which causes stenosis (see Fig. 9 for histologic preparation).

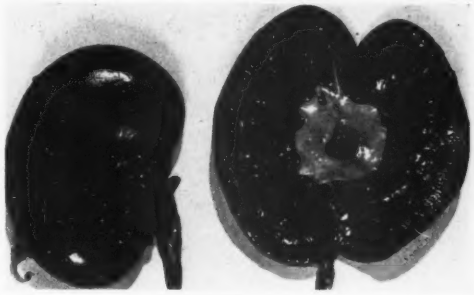

FIG. 5. Kidneys of dog A-7 on the fifth postoperative day. Note slight hydronephrosis.

RESULTS

Ureterocolostomy type I (dogs of series A). Hydronephrosis (grades 1 to 4) occurred in all (Figs. 1, 3, and 5). The mean grade of hydronephrosis was moderate (grade 2) with moderate dilatation and kinking of the ureter. Renal scarring, secondary to pyelonephritis, occurred in almost all animals sacrificed at 4 weeks or later. The dog (A-12) which was allowed to survive longest (145 days) had small yellowish-white calculi in the juxtamural portion of both ureters.

The blood urea nitrogen was normal with low grade hydronephrosis but elevated when the hydronephrosis was grade 2 to 3. The serum creatinine, on the other hand, was only slightly or not at all elevated in grade 2 to 3 hydronephrosis. Bollman and

FIG. 6. Ureterocolostomy of dog A-7 after 5 days. Edema and inflammation at stomas, *S*, producing stenosis shown by bilaterally dilated kidneys and ureters. It is too early for growth of connective tissue at stomas (Fig. 8).

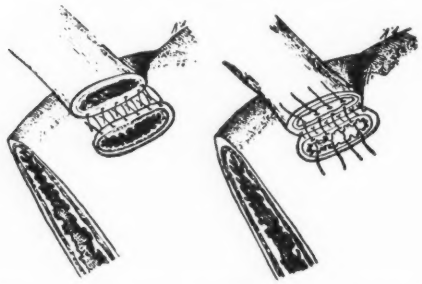

FIG. 7. End-to-side ureterocolostomy according to technique of Chaput as illustrated by Boari. On the left is the seroserosal layer of interrupted sutures and on the right the second, or mucomucosal, layer of interrupted sutures.

Mann have found that when the intestine is perfused with urine by bilateral ureterojejunostomy, the blood-urea rises promptly but the blood-creatinine does not. Conversely, intestinal irrigation has been noted to clear large amounts of urea but little creatinine from the plasma (16). The intestinal wall is thus apparently relatively impervious to creatinine. The dogs all became acidotic, with serum chloride ion and bicarbonate ion of 107 to 127 milliequivalents per liter and 10 to 15 milliequivalents per liter respectively. A sample of chemical data from a dog with bilateral grade 1 hydronephrosis (dog A-10) was as follows on the forty-ninth postoperative day: blood urea nitrogen 72 milligrams per cent; creatinine 0.6 milligram per cent; sodium ion 150 milliequivalents per liter; potassium ion 4.4 milliequivalents per liter; chloride ion 123 milliequivalents per liter; bicarbonate ion 10 milliequivalents per liter; and on the one hundred sixth postoperative day: blood urea nitrogen 41 milligrams per cent; creatinine 0.7 milligram per cent; sodium ion 153 milliequivalents per liter; potassium ion 4.2 milliequivalents per liter; bicarbonate ion 15 milliequivalents per liter; chloride ion not done. Uremia, hyperchloremia, hypernatremia, and acidosis were thus striking in spite of almost normal kidneys.

Slitting the entire ureter longitudinally showed clearly, in all animals, that the ureter was stenosed at only one site. This was at the very mouth of the ureter in the colon. In all instances the stenosis grossly appeared to be due to localized bundle of scar (Figs. 2, 4, and 6*S*). A prominent "bud," "nodule," or "rosette" at the ureteral stoma in the bowel (shown intact in Figs. 4 and 6) was associated with narrowing at the stoma.

Histologic sections, made through the ureterocolostomy, included the distal end of the ureter, ureteral stoma, and adjacent colon. Staining with Masson's trichrome technique differentiated connective tissue (blue) from muscle (red). These preparations demonstrated that luminal narrowing at the stoma is due to overgrowth of connective tissue. Figure 8 is a histologic section through a ureterocolostomy 5 days postoperatively. Although the cut margins of ureter and bowel had been sutured together, there was, between sutures, a relatively large expanse of cut surface of bowel muscle (longitudinal muscle, *LM*; circular muscle, *CM*) and of submucosa, *SM*, which must epithelialize before healing is complete. At 5 days, the free surface of the submucosa, *SM*, and of areolar tissue or adventitia, *AT*, has become covered by flat to cuboidal epithelium. The gross appearance of stomas on the fifth postoperative day is shown in Figure 6, in which the right bud or rosette is intact and the left slit longitudinally. Figure 9 (dog A-2) shows that at 33 days the rosette, *R*, is composed largely of connective tissue which, in this instance, has obviously proliferated from bowel submucosa, *SM*. There is a conspicuous area of inflammatory tissue, *IT*, which is reputed to elicit edema and fibrosis. The connective tissue at the other ureteral stoma of dog A-2 appeared to be continuous with, and may have arisen from, adventitia of the ureter.

On one occasion the obstructing factor, forming the rosette was a whorl of circular muscle of the bowel (Fig. 10*W*) or of circular and longitudinal muscle. In this instance muscle was an obstruction rather than the hoped-for sphincter.

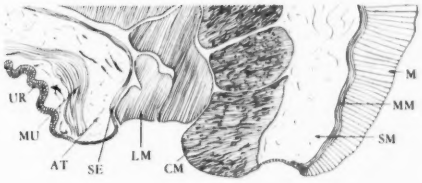

Fig. 8.

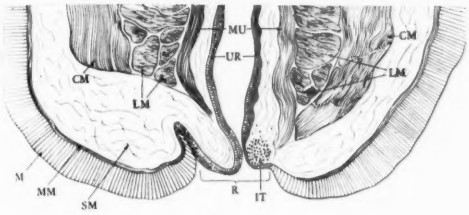

Fig. 9.

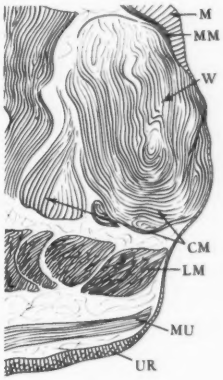

Fig. 10.

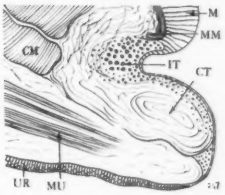

Fig. 11.

FIG. 8. Semidiagrammatic drawing of longitudinal section through ureteral stoma and adjacent colon of dog A-7 (see Fig. 6 for gross specimen). Only one side is shown, Masson's triple stain. *AT*, alveolar connective tissue between ureter and serosa of colon; *CM*, circular muscle of colon; *LM*, longitudinal muscle of colon; *M*, mucosa of bowel; *MM*, muscularis mucosae; *MU*, muscle of ureter; *SE*, serosa of bowel; *SM*, submucosa of bowel; *UR*, urothelium.

FIG. 9. Semidiagrammatic drawing of longitudinal section through left ureteral stoma and adjacent colon of dog A-2 on thirty-third postoperative day (see Fig. 4 for gross specimen). *CM*, circular muscle of bowel; *IT*, inflammatory tissue at mouth of ureter; *LM*, longitudinal muscle of bowel; *M*, mucosa of bowel; *MM*, muscularis mucosae; *MU*, muscle of ureter; *R*, bud or rosette about ureteral stoma; *SM*, submucosa of bowel; *UR*, urothelium.

FIG. 10. Semidiagrammatic drawing of longitudinal section through left ureteral stoma and adjacent colon of dog A-12. Only half of anastomotic area is shown. Key to letters as for Fig. 9; *W*, whorl of muscle from longitudinal muscle of bowel.

FIG. 11. Semidiagrammatic drawing of longitudinal section through ureteral stoma of dog B-1 on twenty-third postoperative day. Only one side is shown (see Fig. 13 for gross specimen). *CM*, circular muscle of bowel; *CT*, connective tissue proliferation at ureteral stoma; *IT*, inflammatory tissue at mouth of ureter; *LM*, longitudinal muscle of bowel; *M*, mucosa of bowel; *MM*, muscularis mucosae; *MU*, muscle of ureter; *R*, ureteral stomal bud or rosette; *UR*, urothelium; *W*, muscular whorl from circular muscle of colon at mouth of ureter.

Ureterocolostomy type II (dogs of series B). Hydronephrosis was moderate to advanced (Figs. 12 and 14). Uremia was greater on the average than with type I. The dogs were sacrificed postoperatively usually while losing ground with anorexia and loss of weight. The anastomoses were studied from the fifth to twenty-third postoperative day. In all instances, the one site of obstruction was at the very mouth or stoma of the ureter and appeared, grossly, to be due to overgrowth of connective tissue (Figs. 13 and 15*S*).

The intraluminal portion of ureter on the fifth postoperative day was only 2 to 3 millimeters long and was covered with greenish slime (Fig. 15). The anchoring suture of No. 5–0 chromic catgut was still intact but attached only to the bowel wall. The intraluminal portion of the ureter had retracted markedly even though the ureter had not been under tension. The narrowest segment of the ureter was at its end or stoma (Fig. 15). Histologic sections, made of the intraluminal portion of the ureter at this stage, were illuminating (Figs. 16 to 19). The surface of the ureteral stoma was an inflammatory membrane (Fig. 16*IM*) consisting of fibrin and many free erythrocytes,

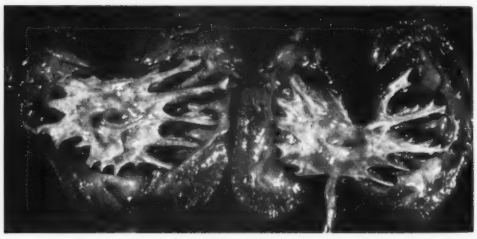

FIG. 12. Kidneys of dog B-1 on twenty-third postoperative day. Bilateral advanced hydronephrosis.

lymphocytes, plasma cells, and granulocytes; there were also capillaries and fibroblasts (Fig. 17). Farther from the surface, in the zone of fibroblastic proliferation (Fig. 16*ZF*), the number of fibroblasts increased and inflammatory cells decreased (Fig. 18). Still more remote was the zone of mature connective tissue (Figs. 16*CT* and 19). The inflammatory membrane was the "green slime" of the gross specimen (as mentioned and Fig. 15).

By the tenth day the intraluminal portion of ureter was a mere bud or dimple in the bowel mucosa. The stenotic ureteral tip was largely whorls of dense fibrous tissue which appeared to arise chiefly from bowel submucosa (Fig. 11; twenty-third postoperative day). The sequence of events appears to be thus: Infected granulating tissue at the tip of the ureter becomes edematous and hemorrhagic (Figs. 15 and 16). Migration and proliferation of fibroblasts into this raw, infected region bring about secondary healing and either cicatrization or stenosis (Fig. 11).

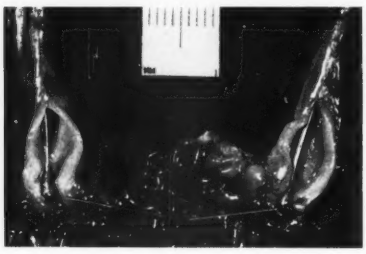

FIG. 13. Ureteral stomas, *S*, of dog B-1 slit open. Note that only constriction is at mouth of ureter where there is rosette: postinflammatory, healed, phase. Dilated tortuosities of ureter not included in photograph.

Ureterocolostomy type III. End-to-side ureterosigmoidostomy was performed on 7 ureters in 8 patients with carcinoma of the bladder (VAH 29114, 26919, 32634, 27076). The eighth ureter was anastomosed to sigmoid by Mathison's technique (VAH 27076; left ureter). Intravenous pyelography, 4 to 5 weeks postoperatively, disclosed either no hydronephrosis or only slight (grade 1) hydronephrosis in 7 kidneys. The ureter which had been anastomosed to sigmoid by Mathison's technique probably stenosed because irreversible moderate hydronephrosis resulted. VAH 29114, who had a Jewett type B urothelial cell carcinoma of the bladder (14) is alive 1 year postoperatively without clinical evidence of tumor. VAH 32634, who had type C squamous cell carcinoma, succumbed to rapid spread of tumor. Extensive pelvic carcinoma prevented histologic evaluation of the anastomosis in that case. VAH 27076 had a type C urothelial cell carcinoma of the bladder and underwent a similar fate as the preceding patient; for a similar reason, histologic evaluation was impossible. VAH 26919 underwent only palliative ureterosigmoidostomy because of stubborn bleeding from a bladder tumor. Bleeding ceased immediately after ureteral transplantation and never recurred. Cystectomy was not justifiable in his case because of concomitant inoperable bronchiogenic carcinoma. He died 2 months after ureterosigmoidostomy from cerebral metastases of bronchiogenic carcinoma. Anatomic and histologic study was possible in this unique case. The ureteral stomas were wide open and without scar. They were remarkably flush with mucosa of the bowel, showing complete absence of bud, nodule, or rosette (Fig. 20*S*). In ureterocolostomy types I and II, it has been noted that the rosette around the stoma is the culmination of deposition of fibrous tissue in an infected, edematous, granulating, raw region. The bud or rosette is thus an undesirable feature.

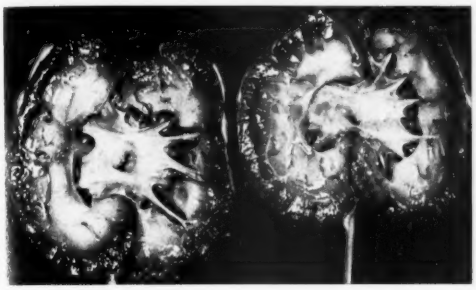

FIG. 14. Kidneys of dog B-6 on fifth postoperative day. Bilateral moderately advanced hydronephrosis.

DISCUSSION

The ureters of many fish, and of amphibians, reptiles, and monotremes empty into the cloaca, a common vestibule with the rectum. The cloaca, at least of the alligator and several birds, according to Hinman and associates (12), teems with bacteria although the kidneys and ureteral urine are bacteria-free. Weyrauch and Hinman (23) indicated that there is no immunizing factor at the ureterocloacal junction because pyelonephritis superimposed upon hydronephrosis after reimplanting the ureters into the cloaca. Anastomosis of the ureters of the chicken to the cloaca without producing hydronephrosis was impossible owing to the small caliber of the ureters which vitiated precise suturing of their cut margin to the artificial stoma in the cloaca. These results, and especially the existence of normal uninfected kidneys and ureteral urine in the intact cloacal animal, emphasize the importance of the anatomic relationship and the necessity for exceeding meticulousness during ureterocolostomy in animals large enough to establish wide open continuity between lumina of ureter and bowel.

When ureter is implanted into bowel so that it presents a free cut margin, as in the type II ureterocolostomy, healing cannot occur by primary intention, i.e., by simple rapid sealing of the defect by epithelium. Vermooten, Hinman and Weyrauch (13), and Riba showed that the free end of the ureter develops granulation tissue and is likely to become inflamed, edematous, and infected. Sloughing of the free ureteral end from deficient blood supply or pressure necrosis from an indwelling metal or plastic tube also disposes to edema and stenosis.

FIG. 15. Ureteral stomas, *S*, of dog B-6 in lumen of bowel. Ureter protrudes into lumen only 2 to 3 millimeters where it is slightly hemorrhagic and covered with greenish slime. Obstruction is confined to mouth of ureter. Demonstrating inflammatory phase; fifth postoperative day.

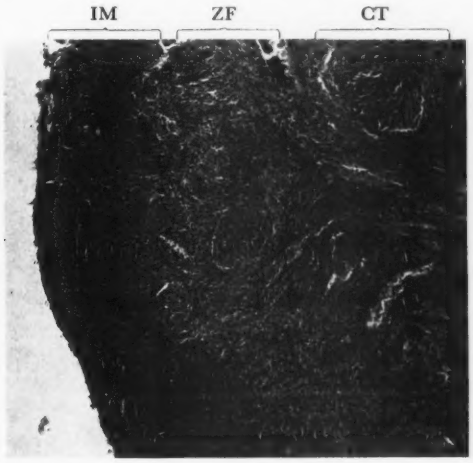

FIG. 16. Photomicrograph of transection through intraluminal portion of ureter of dog B-6 on fifth postoperative day. The free surface at the left is the inflammatory membrane, *IM*, appearing grossly as green hemorrhagic slime. *ZF*, zone of fibroblastic proliferation; *CT*, zone of mature connective tissue.

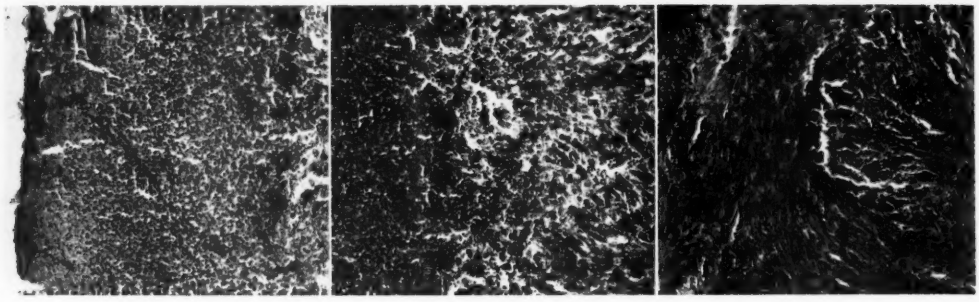

Fig. 17. Fig. 18. Fig. 19.

FIG. 17. Photomicrograph of inflammatory membrane of specimen in Figure 16. It consists largely of fibrin, erythrocytes, and granulocytes.

FIG. 18. Photomicrograph of region immediately adjacent to the inflammatory membrane of Figure 16. It contains erythrocytes, lymphocytes, plasma cells, and granulocytes in ascending order. There are also capillaries and, on the right, numerous fibroblasts.

FIG. 19. Photomicrograph of region of ureter, still farther from the surface, containing largely fibroblasts and mature connective tissue. This represents an enlargement of zone *CT* in Figure 16.

The importance of infection in the production of scarring in the cut end of the ureter was emphasized by Weyrauch and associates (22) who noted little to no stenosis in the free end of the ureter after neoureterocystostomy. This experiment, however, introduces another variable, namely, a different viscus. Submucosa of bowel, as noted in this work, is probably an important contributor of fibroblasts to the ureterocolic junction during healing by secondary intention.

Weyrauch and Young (24) noted that an intraluminal segment of ureter leads to a high incidence of obstruction and suggested that its use be abandoned. Concerning the bud, rosette, or nodule within the lumen of the bowel, Cordonnier (8) remarked that "it was this very finding at autopsy following a Coffey I transplant which led me to do the first mucosa-to-mucosa anastomosis." Riba similarly found that, with mucosa-to-mucosa anastomosis, there was practically no intraluminal bulging at the junction, i.e., no mucosal bud. Woodruff and associates performed the Coffey I anastomosis (i.e., distal end of ureter through submucosal tunnel and free end of ureter held in lumen of bowel by anchor suture) in dogs and postoperatively colonoscoped the animals with the McCarthy cystourethroscope. The tip of the ureter did not slough but swelled into a firm nodule. Histologic sections through this revealed acute and chronic inflammation. Kerr and Colby, in a follow-up of their cases of ureterocolostomy by the type II method of this paper, report that ". . . they all had some hydronephrosis grade 2 to 3; two of them developed small stones which fell into the ureter and had to be operated upon" (9). It is indeed of interest that Baker and associates found that cortisone, in adequate dosage, markedly reduced fibroplasia at the intraluminal portion of the ureter.

FIG. 20. Ureteral orifice, *S*, in lumen of sigmoid of ureterosigmoidostomy by type III technique. Note absence of rosette or bud about ureteral orifice, *S*. The operation had been performed about 2 months prior to demise from cerebral metastases from concomitant bronchiogenic carcinoma.

In rejecting as undesirable the principle of an intraluminal segment of ureter one

includes such procedures even in which there is an indwelling metal or plastic cannula or button, whether or not the ureter passes through an intramural tunnel. One also regards as undesirable the cutting of a ureter in the lumen of the bowel by an electrical snare or other device. Similarly, the sloughing through of ureter by transfixion suture is to be rejected as not conducive to primary union of urothelium and bowel mucosa.

On September 13, 1892, after several rehearsals on the cadaver, Chaput performed his first direct end-to-side ureterocolostomy. It was successful. The anastomosis was done in two layers, the "muco-muqueuse" and the "séro-séreuse," with interrupted sutures (Fig. 11). Finally the juxtamural portion of the ureter was buried in a plication of bowel by the "musculo-musculeuse" set of sutures, like a Witzel enterostomy. Because the mammalian ureter has no mucosa the term "mucosa-to-mucosa" is inexact and should be replaced by "urothelium-to-mucosa." As it is, however, only a few surgeons have considered it desirable to perform the anastomosis precisely as described by Chaput. Suturing today, as indicated by Cordonnier (6, 7, 8), Nesbit (18), Hinman and Hinman (11), and Baker (1), is usually through the entire wall of ureter and mucosa-plus-submucosa of bowel. If No. 5–0 chromic catgut is used with minimal trauma and if the sutures are set only about 1 millimeter apart, mucosa and urothelium will be close together throughout the line of apposition so that primary union between urothelium and mucosa will occur assuming, of course, that the blood supply to the end of the ureter has not been abolished or reduced by rough handling or excessive mobilization of ureter. To reduce incidence of reflux up ureter, Leadbetter, Woodruff and associates, Weyrauch and Young (24), and Nesbit (19) have recently anastomosed the full thickness of the ureter to the mucosa of the bowel in the performance of a submucosal tunnel. Follow-up reports using such a technique have been, in general, favorable. The rosette at the stoma has been eliminated.

SUMMARY

1. Bilateral ureterocolostomy with attempted sphincter formation by a full thickness cuff of wall of the lower colon about the terminal end of the ureter was performed in 12 dogs (type I ureterocolostomy). These were sacrificed after 3 days to several months. The anastomoses were studied microscopically in Masson's trichrome to differentiate connective tissue from muscle. Slight to advanced hydronephrosis, observed in all animals, was evidently due to overgrowth of connective tissue from the submucosa of the bowel or to muscular whorls from the bowel muscle at the junction of bowel and ureter, forming a nodule, bud, or rosette about the ureteral stoma. The bulging connective tissue or muscle whorl at the site of anastomosis was covered by a thin layer of urothelial cells that bridged the gap between urothelium and columnar epithelium of bowel. The surface, in places, was denuded of epithelium and the subjacent connective tissue was covered by fibrin and granulocytes. The nodule, bud, or rosette formed at the stoma was the narrowest portion of the ureter and the only site of stenosis; such a formation is, therefore, considered undesirable.

2. Simple pull-through ureterocolostomy was performed in 6 dogs (type II ureterocolostomy) and studied as above. The ureteral tip became detached from its suture attachment to the intestinal serosa within 5 days. The intraluminal portion of the ureter became lined by an inflammatory zone and then stenosed. By retraction, cicatrization, and, perhaps, slough, the ureteral tip became almost even with the intestinal mucosa. The nodule, bud, or rosette which formed around the stoma was the narrowest portion of the ureter and the only site of stenosis; such a formation is, therefore, considered undesirable. Hydronephrosis tended to be greater in these dogs than in those of type I ureterocolostomy.

3. Full thickness end-to-side anastomosis (type III ureterocolostomy) was performed

in 4 patients on 7 ureters, and 1 ureter was anastomosed by Mathison's method. The latter anastomosis resulted in moderate hydronephrosis, while in the others hydronephrosis was absent or slight. It was feasible to examine grossly and microscopically only one pair of ureteral stomas performed according to type III. The ureteral orifices were quite flush with the intestinal mucosa, there being no bud, nodule, or rosette. Absence of such is desirable.

4. Concluding, it is considered important that the free margin of ureter be sutured to the opening in the bowel wall by closely set, interrupted sutures of fine (preferably No. 5–0) chromic catgut swaged to a round fine needle. In this manner mucosa of bowel will be adjacent to urothelium of ureter permitting rapid union of urothelium and mucosa with minimal interposition of proliferating connective tissue between the cut surfaces of ureter and bowel. Other things being equal, there will be more strength to the suture line when the sutures are passed through the full thickness of ureter and of bowel.

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STUDIES OF THE ABSORPTION AND EQUILIBRATION OF WATER (DEUTERIUM OXIDE) FROM THE GASTROINTESTINAL TRACT FOLLOWING INJURY

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THE PRESENT STUDY of the absorption and equilibration of deuterium oxide from the gastrointestinal tract had as its primary purpose the investigation of the limitations of oral fluid administration to mass casualties. The administration of fluids to mass casualties poses problems which have not been previously explored.

The secondary purpose of this study was to gain factual observations upon which to base routine postoperative care in the field of fluid administration.

Finally, the authors hoped to gain additional information on the nature and scope of the systemic response to injury. Studies by the Surgical Research Team in Korea demonstrated that every organ and system which could be studied, and presumably every cell in the body, responds to severe trauma. In general, this response is not of a few moments' or hours' duration but is a response which lasts for days or weeks. This study was, therefore, designed to extend these observations to the response of the gastrointestinal tract to injury.

Schloerb and his co-workers described an equilibration curve in venous blood following the oral ingestion of deuterium oxide in a human subject. They found an equilibration time of approximately 3 hours. London and Rittenberg also noted a rapid equilibration (40 minutes) in a single subject. Earlier, Visscher and his associates had clearly demonstrated that the movement of water (deuterium oxide) across the ileal membrane was not based on a process of simple diffusion. Cope, in animal experiments, demonstrated a rapid absorption of deuterium from the stomach. Code and his associates extended the studies in normal humans and confirmed the rapid absorption from the gastrointestinal tract.

From the Surgical Research Team in Korea of the Army Medical Service Graduate School, United States Army, in collaboration with the Division of Atomic and Radiation Physics, National Bureau of Standards, Washington, D. C.

MATERIALS AND METHODS

The study was carried out at a forward Surgical Hospital on the Eastern Front in Korea during 1952 to 1953. During this time the average time between wounding and reaching the forward hospital was 3.5 hours.

Healthy young soldiers in noncombat areas volunteered as controls. The wounded subjects were young battle casualties in the 18 to 34 year age range.

Those casualties who were studied immediately after arrival at the hospital were selected on the basis that they had fasted for 5 to 12 hours prior to injury and gastric suction had confirmed the presence of an empty stomach.

Each casualty was given 50 to 100 grams of deuterium oxide (heavy water) as isotonic saline. The deuterium oxide was 99.8 per cent pure.

Venous samples were obtained prior to ingestion and at frequent periods thereafter. Several were studied at 5, 10, 15, 20, 30, 45, 60, 90, 180, and 240 minutes after ingestion. In addition, when feasible, subsequent samples were obtained after a prolonged period of time. Other casualties were, of necessity, studied less intensively but enough points on the equilibration curve were obtained to describe its pattern.

The venous blood was centrifuged, the plasma withdrawn, placed in a paraffin,

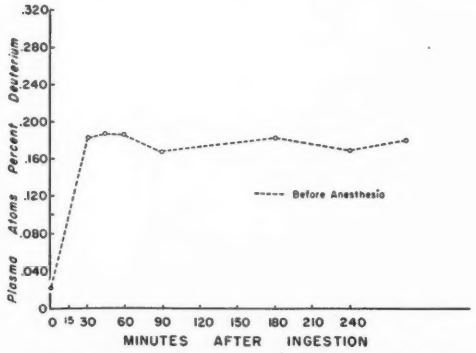

FIG. 1. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in the control subject, demonstrating the very rapid equilibration.

sealed test tube, and shipped via air to Washington, D. C., for analysis.

Deuterium content of the samples was determined by converting the "free water" to hydrogen over hot magnesium with subsequent mass spectrometric analysis of the isotopic hydrogens.

Briefly stated, a few drops of the serum sample were placed in a small flask under a dry nitrogen atmosphere and attached to a vacuum manifold. The serum was quickly frozen with "dry ice" and the flask was evacuated. After isolating the pumps, connection was made to a glass tube furnace filled with carefully prepared magnesium turnings and previously heated to 500 degrees C. in vacuo. A cold finger forming the upper part of the tube furnace was cooled with liquid nitrogen and the "dry ice" removed from the serum flask. Water sublimed from the frozen serum to the cold finger leaving a thin, dry layer of solids in the flask. The tube furnace was then isolated from the manifold and the cold finger permitted to warm up. A glass piston-type pump actuated by a solenoid continuously circulated water vapor and hydrogen through the furnace at 500 degrees C. until no condensed water was observed and pressure measurements indicated very nearly complete conversion of water to hydrogen. A portion of the hydrogen was removed for mass spectrometric analysis.

Serum samples were converted at least in duplicate, and, when practicable, in order of expected increase in deuterium content so as to minimize memory effects in the furnace.

The isotopic analyses were made with a Consolidated 21-103 mass spectrometer using established techniques including operational procedures suggested by Honig. The hydrogen samples were cooled at 190 degrees C. to prevent possible introduction of water vapor. At least 3 determinations were made of each duplicate sample. Analyses of samples containing less than 0.5 atom per cent deuterium were generally repeated if the duplicates disagreed by more than 0.01 atom per cent. The reproducibility of a single determination was usually of the order of 0.003 atom per cent deuterium.

Experiments with nearly pure deuterium oxide indicate the techniques used in the conversion process result in memory effects

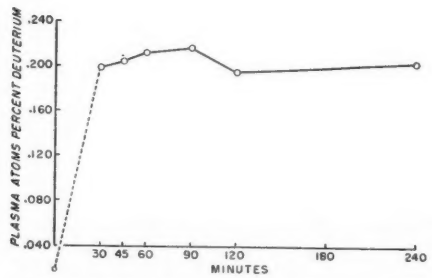

FIG. 2. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in a second subject, demonstrating a similar equilibration curve.

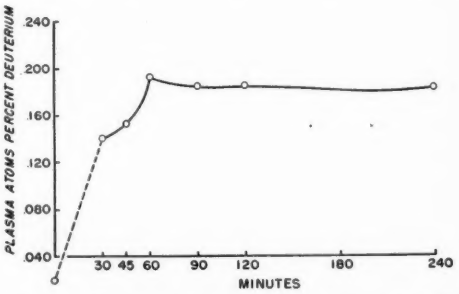

FIG. 3. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in control, demonstrating equilibration within 90 minutes.

of considerably less than 1 per cent. Analyses of test mixtures of hydrogens indicated the mass spectrometer uncertainty to be of the order of 1 per cent for samples containing about 0.3 atom per cent deuterium. However, the necessary delay in receiving, converting, and analyzing the samples undoubtedly contributed to the experimental error. Furthermore, although all samples were intended to be hermetically sealed, a number showed definite evidence of evaporation in transit. Those showing marked evaporation were not analyzed.

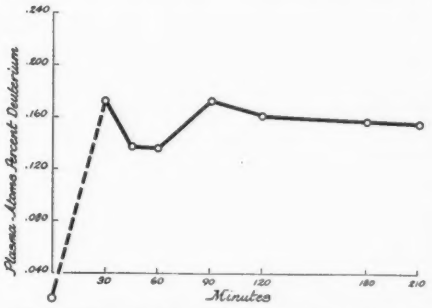

FIG. 5. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in control. Equilibration time 120 minutes.

GASTROINTESTINAL ABSORPTION

In the uninjured soldier. Six healthy soldiers volunteered as controls. All 6 had been fasting for 14 hours and continued to fast throughout the period of study. Each was given 100 grams of deuterium oxide orally.

The results are depicted in Figures 1 to 6. Equilibration of the concentration of deuterium in the venous plasma was complete in 120 minutes. In several instances equilibration appeared to be complete within 90 minutes. Furthermore, without exception, the venous concentration at 30 minutes demonstrated evidence of absorption of an appreciable amount of deuterium.

Absorption of water obviously occurred in the normal and in many of the wounded men. This was demonstrated by control of thirst, maintenance of urinary output, and the solid consistency of the stools. That the curve of absorption is directly related to the curve of equilibration of deuterium oxide has not been absolutely proved. Evidence is presented which suggests that the two are directly related but the term absorption is used with this reservation throughout the paper.

Following injuries of the chest and extremities. Three casualties were selected for study because their wounds did not include abdominal injuries. These 3 men had wounds which were representative of 3 types of injuries seen, namely, perforation of the chest, traumatic amputation of the foot, and a moderately severe flash burn. Emphasis was placed upon studying these men shortly after injury in order to determine their gastrointestinal function in this early period.

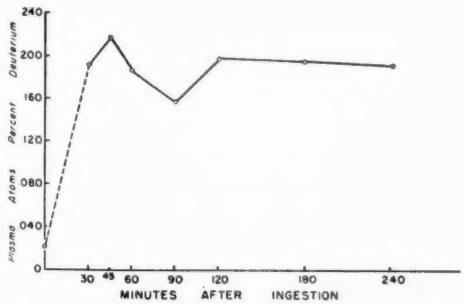

FIG. 4. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in control. Equilibration reached within 120 minutes. The initial rise and fall in concentration have been noted repeatedly and observation appears to be valid in such instances.

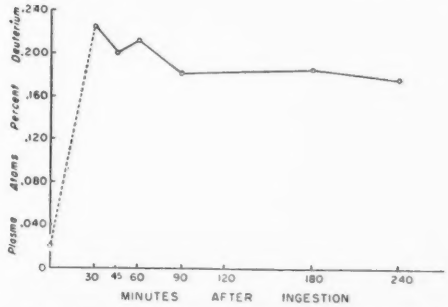

FIG. 6. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in control. Equilibration time approximately 90 minutes. Note, however, the venous concentration is high within 30 minutes after ingestion.

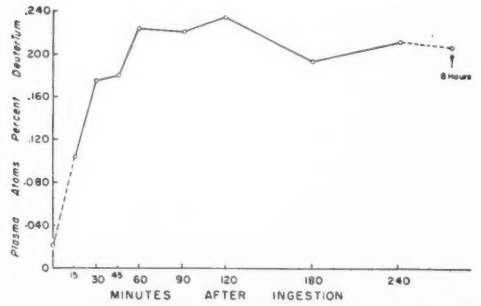

FIG. 7. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 1. This soldier suffered a severe flash burn (second and third degree) of scalp, face, neck, hands, and arms. This study, performed prior to therapy, reveals fairly rapid absorption of water from the gastrointestinal tract as indicated by equilibration time.

PATIENT 1. This 21 year old Korean soldier suffered severe second and third degree flash burns of the scalp, face, neck, hands, and wrists on January 22, 1952. He was admitted to the forward surgical hospital 1 hour after injury. His vital signs were normal except for a tachycardia. His hematocrit was 50 per cent. He had received no therapy at this time.

Three hours after injury and 8 hours after ingestion of food or water, he was given orally 100 grams of deuterium oxide. The venous equilibration curve is demonstrated in Figure 7.

PATIENT 2. This 20 year old South American soldier was wounded on January 17, 1952 by machine gun fire. The bullet penetrated his left lung, producing a large hematoma of the lung but no pneumothorax. He arrived at the forward surgical hospital 3 hours after injury and appeared to be in a state of incipient shock. Débridement of the superficial tissues was performed 6 hours after injury under ether-nitrous oxide anesthesia. His subsequent course was uneventful.

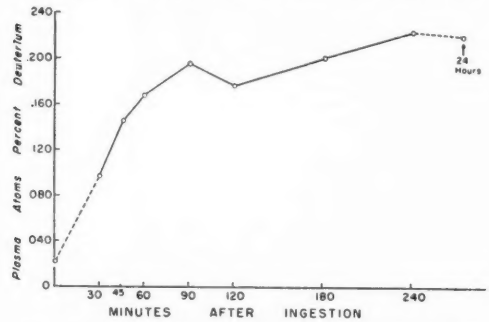

FIG. 8. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 2. This soldier had received a perforating wound of the lung on the previous day. Operation was limited to local débridement of the soft tissues. Note that the equilibration of deuterium, although somewhat slower than normal, proceeds rapidly during the period of study.

After having fasted for 24 hours after injury, he was given 100 grams of deuterium oxide orally. The only medication except antibiotics which he had received subsequent to débridement was 65 milligrams of codeine 7 hours prior to the study.

The equilibration curve of the deuterium is shown in Figure 8.

At the conclusion of the deuterium study, the casualty was given 100 grams of glucose orally. This glucose tolerance study demonstrated the rapid absorption of glucose (Table I). The rising limb of the glucose tolerance curve is very similar to the corresponding phase of the deuterium curve. This suggests that the deuterium was absorbed from the bowel by an active process rather than simply by diffusion.

PATIENT 3. This 34 year old Korean Service Corpsman was injured on May 17, 1952 when he stepped on a land mine. The injury included a traumatic amputation of the right foot above the ankle. In addition, there were penetrating wounds of the left leg and right hand. Hemorrhage from the amputation stump was controlled by a tourniquet.

Two hours after injury he was admitted via helicopter to the forward surgical hospital. His blood pressure was 160/90, pulse 112, hematocrit 40 per cent. He appeared to be severely injured and in a state of incipient shock. Within the first hour after admission, he received 500 cubic centimeters of blood. At this time, 3 hours after injury and prior to operation, a Levin tube was inserted into the stomach and the stomach emptied of a small amount of clear gastric juice. Deuterium oxide, 100 grams, was then instilled through the tube.

Reamputation and débridement were subsequently performed under pentothal-nitrous oxide anesthesia.

By the third postoperative day, his course was smooth. Peristalsis was active and he had had 1 bowel movement since operation. At this time, after fasting for 12 hours, the patient was again given 100 grams of deuterium oxide orally. The results of the two comparable studies are demonstrated in Figure 9.

These 3 soldiers were all severely injured men. They fell into a similar functional pattern. All 3 were treated with oral fluids only. Thirst was controlled and urinary output was maintained by oral therapy. Equilibration was slower than normal in all 3 casualties but was fairly rapid in the first 2. The third soldier had an equilibration rate which was definitely slower than normal, but which increased during the 3 days following injury.

A fourth casualty with gasoline burns of the face, neck, scalp, hands, and wrists was

given glucose (100 grams) orally, immediately after injury and again the following day. On the day of injury, the blood glucose rose from 163 milligrams per cent (fasting) to 314 milligrams per cent after 90 minutes. This observation was repeatedly noted in a study of the metabolic response of the battle casualties and demonstrated the residual absorptive function of the gastrointestinal tract after peripheral injuries.

Following intraperitoneal injuries. Six casualties with intraperitoneal injuries and 1 with retroperitoneal injuries were studied. Two patients were studied immediately after injury and prior to surgery. The others were studied during the postoperative period.

PATIENT 4. This young Turkish soldier was wounded at noon on February 29, 1952 by artillery shell fragments. The fragments penetrated the right chest, including the lung and liver. He arrived at the forward hospital 3½ hours later by helicopter. His blood pressure at this time was 46/20 and he was in a state of severe shock. After 1,500 cubic centimeters of blood his pressure had risen to 70/40 and his blood volume measurement (T-1825 dye method) demonstrated a residual deficit of 19 per cent.[1] At this time, prior to operation and prior to any medication, he was given 100 grams of deuterium oxide orally (Fig. 10). He remained hypotensive throughout the ensuing 30 minutes of the study.

Subsequently, he underwent a right exploratory thoracotomy under nitrous oxide and ether. The diaphragm was opened and the liver was drained subdiaphragmatically. The pleural cavity was drained to an underwater seal.

His subsequent course was smooth. The deuterium study was repeated on the fifth day after injury.

PATIENT 5. This 24 year old American soldier was wounded at 4:35 p.m. on May 10, 1952 by mortar shell fragments. The wound included a massive wound of the right colon necessitating a right colostomy. On admission to the forward hospital, 3 hours after injury, he was in excellent condition. His blood pressure was 120/60, pulse 92 per minute. His plasma volume measurement (T-1824 dye method) demonstrated a deficit of 14 per cent. His hematocrit was 54 per cent.

At this time, prior to operation, he was given 100 grams of deuterium oxide orally (Fig. 11).

After the conclusion of the study, his stomach was emptied and found to contain 32 cubic centimeters of fluid containing only 0.3 per cent of the ingested deuterium.

[1]Normal plasma volume calculated on basis of 45 cubic centimeters per kilogram of body weight.

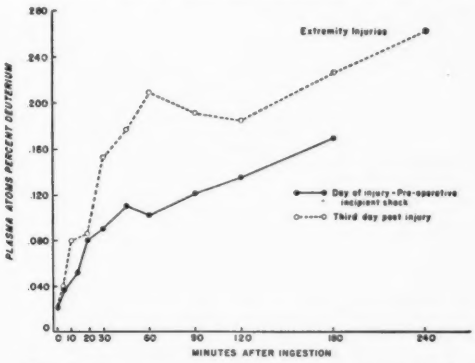

FIG. 9. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 3. This corpsman had severe wounds of the extremities and was in a state of incipient shock when studied prior to therapy. Equilibration proceeded fairly rapidly although slower than it did 3 days later. On the third day after injury, equilibration, although faster, was still slower than normal. A state of equilibration was not reached within 4 hours. Throughout the postoperative period oral intake of water permitted adequate hydration as indicated by lack of thirst and by urinary output. Note that the concentration of deuterium for the second study has been corrected for the residual plasma deuterium concentration from the previous study.

PATIENT 6. This 22 year old American soldier had a perforation of the bowel 6 or 8 hours prior to laparotomy. Operation was performed under nitrous oxide ether anesthesia. He was found to have an advanced peritonitis.

On the first postoperative day, his condition was good. At this time, his blood volume deficiency was measured at 2 per cent. His hematocrit was 49 per cent. He was then given 100 grams of deuterium oxide orally. The study was terminated after 120 minutes when the patient vomited.

The study was repeated on the fourth postoperative day (Fig. 12). By this time, peristaltic activity seemed normal by auscultation.

PATIENT 7. This 21 year old American soldier was shot through the stomach, jejunum, and colon by a

TABLE I.—BLOOD GLUCOSE CONCENTRATION FOLLOWING ORAL ADMINISTRATION OF 100 GRAMS OF GLUCOSE IN PATIENT 2

Minutes after ingestion	*Blood glucose,* mgm. per cent*
0	95
30	177
45	217
60	237
90	165
120	123
180	105
240	71

*Analysis by the Folin-Wu method.

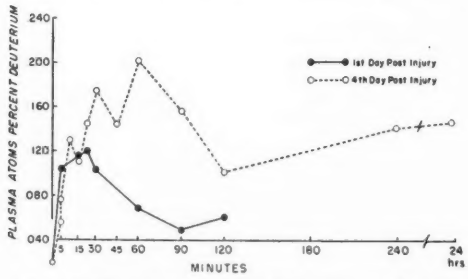

FIG. 10. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 4. This wound did not directly involve the bowel. It consisted of a penetration of the lung and liver with a mild hemoperitoneum. On admission, with the patient in shock, absorption of deuterium was negligible. By the fifth day his bowel activity was clinically normal but his circulatory system remained quite unstable. Absorption had improved but equilibration was not complete after 3 hours. The prolonged period of elevation in plasma concentration may be the result of circulatory inefficiency.

.45 caliber pistol at 3:00 p.m. on January 24, 1952. He arrived at the forward hospital 2 hours later. He was given 500 cubic centimeters of blood prior to operative repair which was done under pentothal, nitrous oxide, and ether. At the beginning of operation, his systolic blood pressure dropped to 90 millimeters of mercury, so he was given a second 500 cubic centimeters of blood.

On the day following injury, his stomach being empty, he was given 100 grams of deuterium oxide through the Levin tube (Fig. 13). At the conclusion of the study, one-third of the deuterium was recovered from the stomach. On the following day the patient developed evidence of a spinal cord paralysis which

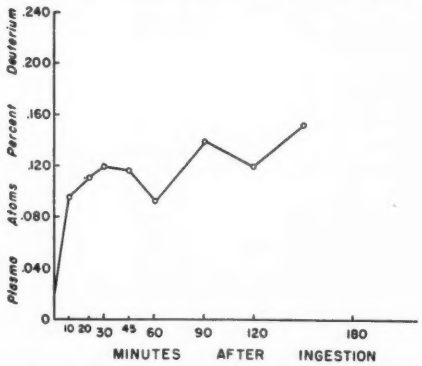

FIG. 11. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 5. The plasma deuterium concentration rose rapidly but equilibration was slow. After 330 minutes, only 32 cubic centimeters of fluid containing 0.3 per cent of the ingested deuterium could be found in his stomach.

was apparently due to indirect trauma from the missile. He became severely hypotensive and died a few hours later.

Autopsy revealed a generalized peritonitis.

PATIENT 8. This 25 year old American soldier was admitted to a forward hospital a few hours following a perforation of the bowel. Laparotomy was performed about 12 hours after injury under spinal anesthesia and the perforation was closed. A widespread peritonitis had developed.

On the first postoperative day his temperature was 99.8 degrees orally, pulse 100, respiration 20 per minute. No peristalsis could be heard. His stomach having been emptied via a Levin tube, he was given 100 grams of deuterium oxide through the tube.

His plasma deuterium curve is demonstrated in Figure 14.

PATIENT 9. This 21 year old American soldier was wounded at 2:30 a.m. on February 21, 1952 when shot through the abdomen with a carbine. The missile perforated the jejunum and the colon. On admission to the forward surgical hospital by ambulance at 8:00 a.m., his blood pressure was 70/60, pulse 124 per minute. The perforation of the small bowel was closed and a colostomy was performed.

Peristalsis became audible on the fourth day after injury and by the sixth day after injury his bowels were moving normally. His oral temperature still rose to 102 degrees daily for several days thereafter.

By the tenth day after injury he was afebrile and his bowels had been moving normally each day for the preceding 7 days. At this time he was given 100 grams of deuterium oxide orally. The resultant curve of plasma deuterium concentration is demonstrated in Figure 15.

PATIENT 10. This 41 year old Korean Service Corpsman was wounded in the back by mortar shell fragments at 1:00 p.m. on January 15, 1952. On admission to the forward hospital his blood pressure was 64/40, pulse 100, respiration 18 per minute. The wounds were explored a few hours after injury under pentothal, nitrous oxide, and ether. Each kidney had been penetrated by the missiles but the abdomen had not been injured.

His vital signs stabilized and his subsequent course was smooth. Bowel sounds were absent for a few hours but returned by the second day after operation. At this time he was given orally, 100 grams of deuterium oxide mixed with 10 grams of glucose (Fig. 16). After 4 hours, the concentration of deuterium in the gastric fluid had decreased to 3 per cent. His blood sugar rose from 127 milligrams per cent, fasting, to 352 milligrams per cent after 45 minutes. After 4 hours only 5 per cent of the glucose could be recovered from the stomach.

DISCUSSION

The studies of the 6 normal subjects (Figs. 1 to 6) demonstrate the rapid equilibration

of water (deuterium) following its ingestion. Equilibration appears to occur in the normal man within 2 or 3 hours after the ingestion of 100 grams of deuterium oxide, an observation which confirms this finding in the subject reported by Schloerb and associates.

The equilibration curve reflects the effects of peristaltic activity, gastrointestinal absorption, intravascular circulation, and diffusion throughout the extracellular and intracellular fluids. The summation of these dynamic processes normally permits equilibration to occur very rapidly.

The study of the first 3 battle casualties demonstrates, as a preliminary observation, that following rather severe injuries to the chest or extremities, or burns of moderate extent, equilibration is delayed.

The delayed rise in venous deuterium concentration in these patients represents a decreased rate of absorption for when deuterium oxide is given intravenously to the injured man, it leaves the circulation more slowly than in the normal man.

Patient 3 (Fig. 9) demonstrates that 3 hours after injury the absorption of water was slower than normal. Three days later, the rate of absorption had increased but was still slower than normal. This impairment in absorption is quite definite and unexpectedly prolonged. When the study was repeated on the third day, the patient had peristalsis which was normal by auscultation. He had also had a normal bowel movement.

The rapid rise in blood glucose concentration following the ingestion of glucose strongly suggests an active absorption process rather than a process of passive diffusion for numerous studies have shown that such an active process is normally responsible for the transfer of glucose across the bowel membrane. This observation appears valid in spite of the fact that under these circumstances glycogen deposition is known to be retarded.

Although in these first 3 casualties the absorption of water did not appear to be normal, the deficiency was not great. All 3 patients were maintained on oral fluids only and this therapy controlled their thirst and maintained an adequate urinary output. Further study is necessary but these studies, backed by clinical experiences, suggest that most such patients can be treated effectively by the oral administration of water.

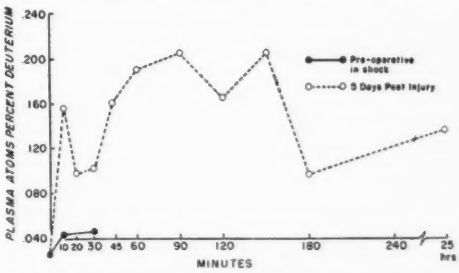

FIG. 12. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 6. This casualty had a severe peritonitis. Equilibration, after 2 hours, had not been approached on the first day after injury. By the fourth day, there had been a marked clinical improvement as well as an improvement in deuterium absorption. Note, however, that compared with the concentration after 24 hours, equilibration had not been reached after the first 4 hours. Again, a prolonged period is observed during which the deuterium is entering the plasma faster than it is leaving. Note that in the graph, the deuterium concentration for the second study has been corrected for the residual deuterium from the earlier study.

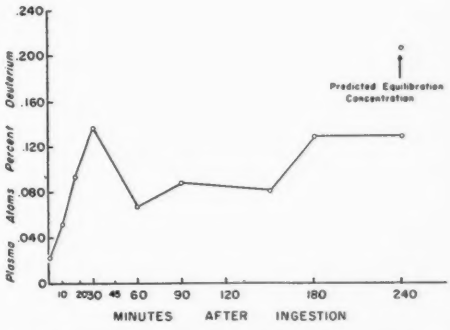

FIG. 13. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 7. This casualty had an unstable circulatory system as well as a marked paralytic ileus. He died the following day with peritonitis. Note that his plasma deuterium concentration after 4 hours was only 60 per cent of the predicted concentration, based on estimate of body water at 63 per cent of body weight. Also a third of the deuterium was still present in his stomach at the conclusion of the study.

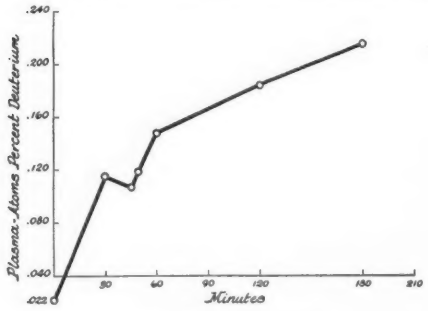

Fig. 14.

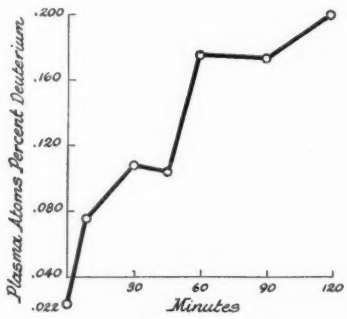

Fig. 15.

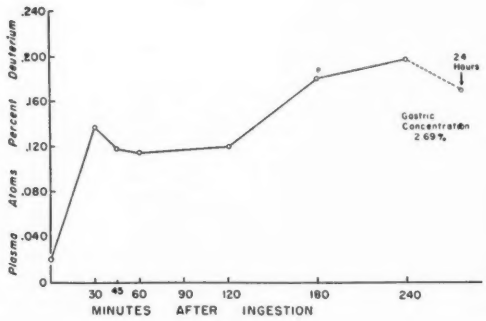

Fig. 16.

FIG. 14. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 8 with paralytic ileus. Although the plasma deuterium concentration rose steadily for 3 hours, equilibration had not yet been reached on the first day after injury.

FIG. 15. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 9. This casualty had had a severe abdominal injury with peritonitis. At the time of this study, on the tenth day after injury, his gastrointestinal function had been normal, as determined clinically, for 7 days. Note, however, the residual marked delay in absorption of water.

FIG. 16. Venous plasma deuterium concentration after oral ingestion of deuterium oxide in Patient 10. This casualty had a wound limited to the kidneys and retroperitoneal area. His clinical course was benign. Peristalsis became clinically detectable on the day of this study (the second postoperative day). Four hours after ingestion of the deuterium, equilibration was not complete. This casualty had 100 grams of glucose instilled into the stomach with the deuterium oxide (300 cubic centimeters total). The glucose tolerance curve was diabetic in form, paralleling the deuterium curve. Four hours after ingestion 5 per cent of the glucose and 3 per cent of the deuterium were recovered from the stomach. This might again suggest an active absorptive function of the gastrointestinal tract at this time.

Certainly, in the treatment of mass casualties, water must be given orally to such patients unless anesthesia is impending.

Following injury to the abdominal viscera, the delay in absorption and equilibration was often quite marked. When superimposed on injury, hypotension was associated with a profound deficiency in absorption (Fig. 10). The deficiency in absorption was present immediately after injury and persisted throughout the first few days thereafter. Like the function of the kidney, liver, and other organs, the function of the gastrointestinal tract was slow to return to normal. As with the other organs, the function had not returned to the normal state even when function appeared normal by clinical observations. Thus Patient 9 demonstrated a residual deficiency in the absorption of water as late as 7 days after the resumption of daily bowel movements. Absorption was definitely occurring as his stools were formed instead of liquid. The equilibration curve, however, demonstrated a delay.

During the early period after abdominal injuries, peristalsis was usually inaudible. Nevertheless, the occasional peaking in the curve of plasma deuterium concentration (Fig. 10) suggests the activity of intermittent peristalsis and raises the question as to whether the basic defect underlying the slow equilibration is primarily in motility rather than the absorptive process per se. Clinical experience with advanced paralytic ileus, however, has demonstrated numerous instances in which the entire bowel was filled with fluid and a defect in the absorptive process was obvious.

Whatever the underlying mechanism, the soldiers with abdominal injuries absorbed water quite slowly following its oral administration. They often vomited if given water orally in appreciable quantities. Anesthesia and laparotomy had to be performed at the earliest feasible date. Motility was reduced and the bowel was often found to be distended with unabsorbed fluids. Thus even under the compromises necessary in the treatment of mass casualties, the oral administration of fluids has no place in the early treatment of patients with major intra-abdominal injuries.

SUMMARY

As measured by deuterium equilibration curves, water rapidly enters the blood from the gastrointestinal tract of the normal man. Equilibration of deuterium throughout the body appears to occur in the normal man within 2 or 3 hours after the ingestion of 100 grams of deuterium oxide.

Preliminary studies indicate that, following burns of moderate extent or severe wounds of the chest and extremities, deuterium absorption is impaired but remains much more rapid than after an abdominal injury.

Following intra-abdominal injuries, deuterium absorption from the gastrointestinal tract is markedly delayed. This function may still be impaired as late as 10 days after injury and as late as 7 days after the resumption of "clinically normal" gastrointestinal function.

Peripheral vascular collapse due to an intra-abdominal injury is associated with only a negligible absorption of deuterium.

The rapid fall in concentration and total amount of deuterium and glucose in the upper gastrointestinal tract following their oral administration and the concurrent rise in blood glucose concentration, as well as in plasma deuterium concentration, suggests that an active absorption process is functioning rather than a process of simple diffusion. The control of thirst, the solid nature of the stools, and the maintenance of urinary output prove that water is being absorbed in all patients except those with acute abdominal injuries.

CONCLUSIONS

The healthy unwounded soldier absorbs water (deuterium oxide) rapidly from the gastrointestinal tract. Gastrointestinal absorption of deuterium oxide is slightly retarded after injury to the chest, extremities, or after burns. Following intra-abdominal injuries, absorption of deuterium oxide from the gastrointestinal tract is markedly retarded for several days. These studies suggest that, in the compromises which may be necessary in the treatment of mass casualties, water may be given orally at any time following injury provided there is no intra-abdominal injury, anesthesia is not anticipated for the immediate future, and the casualty is not comatose. Even under conditions in which mass casualties must be treated, oral fluid therapy to the casualty with major abdominal injuries should be avoided during the first few days following surgery.

The response of the gastrointestinal tract to trauma, like the response of every other system and organ in the body, is a response of tremendous magnitude for a long period of time.

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GASTROSCOPIC OBSERVATIONS FOLLOWING VARIOUS TYPES OF SURGERY FOR GASTRODUODENAL ULCER

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IN THIS ARTICLE are presented gastroscopic, i.e., gross anatomic, observations made after various types of gastric operations. It must be realized that a gastroscopic examination yields results superior to those obtained by inspection of gross specimens because at gastroscopy living tissue is seen with brilliant variegated color. In contradistinction, inspection of the bloodless excised specimen reveals only a uniform dirty grayish pink color. If the gastroscopic findings are compared with microscopic sections, obtained surgically and preserved quickly, a really astonishing congruence is found. This is not true if superficial biopsies are obtained with a suction biopsy tube, as described by Wood and Tomenius, or with the Benedict operating gastroscope. Microscopic specimens thus gained are too small and often too superficial and do not represent the gastroscopic picture.

Only an anatomic description of pictures will be given. No attempt will be made to correlate these pictures with clinical symptoms. Naturally the majority of patients were referred for gastroscopic examination because of symptoms. These were severe enough to induce the patient to submit to an examination considered to be uncomfortable and often expensive. However, quite a few patients had routine gastroscopic checks which were performed for follow-up and for research purposes.

The case material, comprised of patients having had gastroenterostomies and resections of the Billroth II type and its modifications, is large. The gastroenterologist cannot help feeling worried when he considers the large number of patients seeking help for the after-effects of such procedures, even though he naturally does not know what percentage of the total of such operations they constitute. In any event, there are too many such patients.

The number of patients having had vagotomy, either alone or combined with other procedures, is much smaller. This is probably so either because vagotomy is a relatively newer procedure or, possibly, because patients with such operations may not have so many after-effects.

There are only 2 cases of the Billroth I type of resection in our series. It seems that this procedure is rarely performed. However, it is the only one of the resection techniques in which the continuity of the stomach and duodenum is maintained. Other operations which permit ingested food to pass through the stomach and duodenum before entering the jejunum are the pyloroplasty, now often done together with vagotomy, and the wedge excision of a gastric ulcer together with pyloroplasty. Both these types of surgical procedures are contained in our case material. There is, however, an important difference between the Billroth I operation and pyloroplasty. In the Billroth I operation the pyloric muscle is removed, whereas in the pyloroplasty operation it is preserved, although widened. The possible significance of this difference will be discussed later.

OBSERVATIONS

Gastroscopy was done in 368 patients subsequent to surgery of the stomach. In quite a few of these patients multiple gastroscopic observations were carried out. These observations revealed constantly changing pictures and have been described previously.

Here only the gastroscopic findings noted at the first examinations performed on such patients are listed. In 186 patients only a gastroenterostomy was present. One hundred forty-eight patients had had a gastric resection for either duodenal or gastric ulcer or gastric carcinoma or gastric syphilis, 147 being of the Billroth II type and 1 of the Billroth I type. In the majority of cases extensive resections had been performed (Table I). In 34 patients a vagotomy had been done (Table II). Vagotomy without any additional operation had been done in only 8 cases, and in 3 of them the vagotomy was proved to be incomplete. In 26 cases some other operation had been performed in addition to vagotomy, namely resection in 3 cases (2 Billroth II and 1 Billroth I), gastroenterostomy in 11 cases, pyloroplasty in 8 cases, and wedge excision of a gastric ulcer plus pyloroplasty in 4 cases.

Some physiologic disturbances in the postoperative stomach do not appear in this anatomic analysis, viz., impairment of motility, dumping syndrome, and anacidity.

The chief interest of the surgeon is focused upon the recurrent or marginal ulcer, unjustly so, as will be shown presently. Such ulcers were found in 28 of the 186 patients with a gastroenterostomy (15 per cent). They were found in 15 of the 148 patients with gastric resections (10.1 per cent). Here it must be considered that there were a few patients who had had resection for carcinoma and for gastric syphilis in whom recurrent or marginal ulcer could not be expected. Three times an ulcer was found in a symptom-free patient who was examined gastroscopically for the purpose of follow-up.

In the general group of the 34 patients who had had a vagotomy no ulcer was seen. The material is naturally still small and it may be doubted that the complete absence of ulcers is significant. It is well known that recurrent ulcer does occur after vagotomy, although in most of such cases the vagotomy probably has been incomplete.

Recurrence of an ulcer or formation of a marginal ulcer naturally constitutes a major medical problem. Yet relatively few ulcers were found in the 334 patients who had had gastric surgery without vagotomy, namely 43 (12.9 per cent). The great majority of the other patients—291 (87.1 per cent)—had symptoms and many of them had severely distressing symptoms, such as postprandial pain, nausea, and vomiting; yet they had no demonstrable ulcer either gastroscopically or on x-ray examination. If we omit 1 case of gastrocolic fistula, 7 of recurrence of carcinoma, and 1 of syphilitic scarring, 282 cases remain. Of these only 43 showed a normal gastroscopic picture (15.3 per cent). Only 22 patients appeared normal after gastroenterostomy (186 cases, 11.8 per cent), and only 21 patients after resection of the Billroth II type (147 cases, 17.95 per cent).

In all other cases inflammation was seen (84.7 per cent)—gastritis secondary to gastric surgery. The inflammation was either present throughout the entire stomach or it

TABLE I.—GROUP I, GASTROENTEROSTOMY AND RESECTION IN 334 CASES

	Gastroenterostomy	*Resection Billroth II and modifications*	*Resection Billroth I*	*Totals*
Normal mucosa	22	21	—	43
Gastritis				
Mild	60	50	—	110
Severe	68	42	1	111
Of stoma with jejunitis	6	12	—	18
Ulcer				
Without gastritis	7	5	—	12
With gastritis	21	10	—	31
Gastrocolic fistula	1	—	—	1
Carcinoma	1	6	—	7
Gastric syphilis	—	1	—	1
Total	186	147	1	334

TABLE II.—GROUP II, VAGOTOMY IN 34 CASES

Type of vagotomy	*Total*	*Normal mucosa*	*Gastritis Mild*	*Gastritis Severe*	*Ulcer*
Alone, complete	5	5	—	—	—
Alone, incomplete	3	—	3	—	—
With wedge excision of a gastric ulcer and pyloroplasty	4	1	3	—	—
With pyloroplasty	8	5	3	—	—
	20	11	9	—	—
With gastroenterostomy	11	4	1	6	—
With resection Billroth II and modifications	2	—	—	2	—
With resection Billroth I	1	—	—	1	—
	14	4	1	9	—

was located chiefly around the stoma, rarely involving the jejunum. For practical purposes it seemed useful to group these inflammations into two categories, namely into mild gastritis of the type ordinarily seen and the extremely severe gastritis seen only in the postoperative stomach. Those inflammations which chiefly involved the stoma were all of the severe type.

In mild gastritis a mixed form is usually seen; superficial changes and hypertrophic and atrophic areas may be present, and sometimes large areas of atrophy. Although these symptoms do not impress the inexperienced observer too much, we believe that they may be responsible for the manifold distress of the patient.

Such mild gastritis was seen in 60 of 186 patients with gastroenterostomies (32.3 per cent) and in 50 of 147 patients with resection of the Billroth II type (34 per cent).

The pictures seen in the severe form of gastritis, including inflammation of the stoma and jejunum, are much more impressive. They occur only after operations for ulcer and even the inexperienced observer is struck by the extremely severe changes. The mucosa presents a dull angry red appearance, seen in no other condition, and is swollen and sometimes markedly edematous, sometimes covered with purulent exudate, and often presents a number of superficial erosions. Since first described by the senior author in 1922, all gastroscopists have agreed that these changes are unique. Hertel and Kallius proved, by comparison of microscopic sections of resected stomachs with the subsequent gastroscopic findings, that these severe inflammations are not present before the operation but develop after it. Moutier observed patients gastroscopically before and after surgery and stated that the severe type of inflammation is secondary to the operation. Henning wrote: "The gastritic changes in the postoperative stomach belong to the most severe that one can visualize anywhere." Moersch, who saw a normal gastric mucosa in 30 per cent of patients with postoperative symptoms, found that gastroscopy in many cases will reveal severe gastritis. Gutzeit and Teitge stated that "the mucosal changes are in no other form of gastritis even approximately as severe (as in that of the postoperative stomach), so that today . . . this gastritis must be considered chiefly responsible for the distress of patients after gastric operations. Abnormal swelling of the stomal ring . . . grotesque swellings and contractions of folds, causing bizarre . . . forms of the mucosal relief; hypertrophic, granular, verrucous and polypoid formations; dusky red discolorations and a great inclination to hemorrhage: these are the impressive signs of the severe mucosal changes of the postoperative stomach." We must concur with this description. We have repeatedly seen the occurrence of dangerous gross hemorrhages in such cases. At gastroscopy of such patients during the gross hemorrhage we have seen the blood oozing profusely from the swollen hypertrophic mucosa.

This severe type of inflammation was found in our material in 74 of the 186 patients with gastroenterostomies (39.8 per cent), in 54 of 147 patients who had undergone resection of the stomach of the Billroth II type (36.7 per cent), and in 1 patient following a Billroth I type of resection. No one who examines such a stomach can possibly doubt that these monstrous changes are responsible for the patient's distress.

In 1923 the senior author pointed out that a normal gastric mucosa after gastroenterostomy was usually seen when the artificial stoma had acquired a rhythmic pylorus-like activity. He speculated that such rhythmic activity would prevent the unregulated reflux of noxious intestinal juice into the stomach and thereby inflammation. Later the observation was extended to resected stomachs. Christiansen has rejected the validity of these observations. Our present studies, however, seem to confirm them; almost all stomachs with normal mucosa showed the rhythmic adaptation and function of the stoma.

Although the knowledge of this disease is now 32 years old it has escaped the attention of the surgeons. There are some notable exceptions, but to the best of our knowledge only one surgeon has tried to do something about it. Steinberg has devised a modification of gastric resection by means of which reflux of intestinal juice into the stomach may be averted. It is not yet known whether this operation fulfills its purpose.

This disease is scarely mentioned in the general surgical literature. In extensive surgical statistics its existence is barely, or not at all, admitted. This omission must be explained by the fact that surgeons rarely look into the stomach of their patients after operations. We believe that the surgeon would obtain a much clearer picture of what he is doing when he operates upon the stomach if he would, himself, routinely perform gastroscopic examinations before and several months after the operation.

It was interesting to study the postoperative gastritis in patients after vagotomy. These patients had to be divided into two groups, namely those with undisturbed continuity of stomach and duodenum and those in whom the continuity was disturbed by a gastroenterostomy or a resection.

In the latter group—vagotomy plus gastroenterostomy or resection—consisting of 14 cases, severe gastritis was found 9 times (64.3 per cent), certainly no improvement as compared with the group in which gastroenterostomy or resection alone was done.

This acute condition was not found in a single instance of the 20 cases in which a vagotomy was done without the creation of a new stoma and without removal of the pylorus. There were 5 instances of complete vagotomy, 3 of incomplete vagotomy, 4 of wedge excision of a gastric ulcer plus vagotomy plus pyloroplasty, and 8 of vagotomy plus pyloroplasty. Although the characteristic severe gastritis was absent in this group, mild gastritis characterized by mild localized swelling or some adherent mucus was found in 9 cases.

Of special interest are the 2 cases of Billroth I resection, one of them being in the group without vagotomy, the other in the group with vagotomy. In both cases severe gastritis was found. Without these 2 cases one might be tempted to assume that the mere preservation of the normal continuity of the stomach and duodenum would prevent development of severe gastritis. In the Billroth I resection this continuity is preserved. The chief difference between this operation and vagotomy, after which our 20 patients were free of the severe type of gastritis, is that in the Billroth I resection the pylorus is sacrificed while in the other operation the pylorus is not removed. We cannot draw definite conclusions from only 2 cases. However, this observation seems to suggest that it is indeed the unregulated reflux of intestinal juice which causes the severe type of gastritis.

Still another observation substantiates this theory. In 4 patients having a gastroscopically proved severe symptom-producing gastritis following gastroenterostomy, the gastroenterostomy, in consequence of the aforementioned theory, was taken down and a pyloroplasty procedure was substituted. Gastroscopic observation became possible also after that second operation. The gastritis then was noted to have disappeared and the patients were symptom-free.

Once more it must be stated that the material comprising the vagotomy group is still small. If our observations can be confirmed in a larger number of such patients, the conclusion must be drawn that vagotomy with pyloroplasty is much superior to vagotomy with gastroenterostomy or resection and certainly also much to be preferred to gastroenterostomy or resection alone insofar as the postoperative state of the gastric mucosa is concerned.

SUMMARY

1. Gastroscopic observations of 368 patients subsequent to gastric operations are described. Gastroenterostomy was performed in 186 cases, gastric resection (group I) in

148 cases, and vagotomy, partly in conjunction with other procedures (group II), in 34 cases.

2. In the first group a total of 43 ulcers was found (12.9 per cent); in the second group no ulcer was observed.

3. Gastritis was seen in 239 cases of the first group (71.5 per cent) and in 19 cases of the second group (55.9 per cent).

4. A characteristic extremely severe gastritis was seen in 74 (39.8 per cent) of the 186 cases in which gastroenterostomy had been performed and in 54 (36.5 per cent) of the 148 cases in which resection of the stomach had been done. This disease was found in 9 (64.3 per cent) of the 14 cases in which vagotomy was combined with gastroenterostomy or resection. It was totally absent in 20 cases in which the pylorus was preserved and no artificial stoma was present (vagotomy alone, or vagotomy with wedge excision of a gastric ulcer plus pyloroplasty, or vagotomy plus pyloroplasty). This severe form of gastritis is considered to be the most serious disease following surgery for gastroduodenal ulcer.

5. Two patients after Billroth I resection presented severe gastritis. In 4 patients with gastroenterostomy severe gastritis disappeared after the gastroenterostomy had been taken down.

6. It would appear that severe postoperative gastritis can be prevented if the pylorus is preserved and if no artificial stoma permits unregulated reflux of intestinal juice into the stomach.

7. The material on vagotomy is still too small to permit final conclusions. However, at the present moment it would seem that vagotomy with pyloroplasty is superior to other operations for gastroduodenal ulcer insofar as the postoperative state of the gastric mucosa is concerned.

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MITRAL STENOSIS AND COMMISSUROTOMY

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THE PRESENT ARTICLE is not concerned with the historical aspects of the development of commissurotomy for mitral stenosis. More than 50 years ago the theoretic bases for this operation had been proposed by Samways, Brunton, McKenzie, Cushing and Branch, Bernheim, and many others. Renewed interest in this surgical attack has been possible over the past 7 or 8 years because of the work of Harken, Bailey, and Brock (2). Following their lead, the surgical technique of enlargement of the stenosed mitral valve was sufficiently well established to be applied in a large number of cases. For this reason, since February 1950 we have operated upon over 100 cases. The observations reported herein are based on an analysis of our first series of 100 consecutive cases operated upon in Notre-Dame Hospital in Montreal (including 4 cases operated upon in the Queen Mary Veterans' Hospital). The indications for this operation will not be reviewed as they have been covered previously (9) in a publication with our medical confreres, whose precious aid is indispensable to a cardiac surgery team for the selection and preparation of patients.

COMMISSUROTOMY VERSUS VALVULOTOMY

We have deliberately chosen and accepted the term of "commissurotomy" suggested by Durant of Philadelphia, as opposed to the term "valvulotomy" or "valvotomy" proposed by Brock (2), Cooley and deBakey, or even the term of "valvuloplasty" applied by Harken to the digital fracture of the mitral commissures. The object of the operation is *not* to section the leaflets or remove portions thereof but rather to obtain, ideally and selectively, fracture or section in the axis of the commissures (lateral or median) which have become fused, without damage to the anterior or posterior leaflets themselves.

It is indeed unfortunate that confusion as regards the terminology has slipped into the literature, and for this reason we believe it useful to recall that surgical enlargement of a mitral stenosis must have as its aim the *separation* of the fused commissures. Therefore, the term of commissurotomy appears to us not only logical but acceptable.

STATISTICAL ANALYSIS OF 100 CASES

The 100 consecutive patients operated upon have been grouped according to the proposed classification of the American Heart Association for the grouping of stages of this disease. This classification is far from ideal when studying surgical indications or postoperative results. It is not designed to take into account the many factors influencing the surgical decision and many more influencing the postoperative condition. It is for this reason that our group is at present working out a different classification for surgical cases, aiming to group the patients objectively on a basis of numerical factors. It is hoped in this way better to assess the surgical risk as well as the postoperative result. This new proposal of surgical classification of mitral stenosis will shortly be presented (7), but pending its official presentation and acceptation the study of our first 100 cases is based on the classification of the American Heart Association as already mentioned.

A study of our statistics reveals that in stage I of the disease, i.e., at the asymptomatic stage, we do not suggest operating on the patient. A number of surgeons, mostly in the United States, believe that surgery is

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TABLE I.—COMPARISON OF COMMISSUROTOMY TECHNIQUE IN 100 CONSECUTIVE CASES

Type	*Mitral Valve*		*Total*
	Calcified	*Not calcified*	*Per cent*
Instrumental	9	8	17
Digital	7	36	43
Combined	16	24	40
Total	32	68	100

indicated as soon as there are auscultation signs of mitral stenosis without symptoms. We do not share this point of view, as we find it difficult to accept the surgical risk in a patient without symptoms. On the other hand, the patients in stage II are those presenting a pure mitral stenosis with some symptoms mostly on exercise, i.e., dyspnea and signs of stationary decompensation. Fifty-six of our patients were in this category (Fig. 1). We believe that this is the ideal group for surgery. It is in this group that one finds the largest percentage of excellent results and inversely the lowest postoperative mortality, notably 3.6 per cent in our figures. The patients in stage III are worse risks, presenting most often subacute pulmonary edema with occasional paroxysmal attacks and progressive cardiac decompensation. Nevertheless, with adequate preparation, the results are still sufficiently good to justify proposing the operation, even though in our hands the operative risk is much higher—in the neighborhood of 25 per cent.

The patients in stage IV of this classification are the problem cases. Many times the surgical decision is one that rests heavily on the shoulders of the medical and surgical team. These patients are often cardiac invalids with right ventricular failure, sometimes with definite signs of myocardial failure to a degree that would place them in a "bad risk" category, even for other more minor surgical procedures. We do not deliberately suggest operating on this kind of patient, and in the 11 cases that we have done the patients have been warned of the risk involved and have decided to accept the operation only after due consideration in view of the great improvement that could be anticipated following a successful surgical approach. It is evident that in this group of patients the operative risk is very high, and in our statistics the mortality has been 45 per cent.

In summary, on a total of 100 consecutive patients operated upon, 67 per cent showed excellent results, 18 per cent mediocre results, and by this we mean that the patients have continued to exhibit relative disability though the majority of the 18 per cent tell us that they have been sufficiently improved to be satisfied with the operation. (These assessments have been established by the cardiologists themselves and not by the surgical team.) The postoperative mortality in the whole group is 15 per cent which, of course, includes the very early cases when lack of experience, medical as well as surgical, certainly influenced the results. There is no doubt in our mind that patients in stage IV, in whom we suggest operation today, are probably running a risk below that of the 45 per cent illustrated on the chart, because the medical-anesthetic-surgical team has now gained sufficient experience to protect the patient from many complications which the team has faced over the past 4 years.

TECHNICAL CONSIDERATIONS

Carotid compressions. We were sufficiently alarmed by the complication of cerebral embolization both during and following operations (10 per cent) that for the past 2 years we have felt justified in attempting means to prevent this complication or the damages resulting from it. Some surgeons have advocated dissection of the carotid vessels in the chest during the operation and the application of temporary tourniquets during the manipulations of the auricle or the intracardiac exploration. We have thought that such a dissection would prolong operating time and was not without danger, especially if the carotid tourniquets were forgotten temporarily in the face of an emergency. It was, therefore, believed safer to adopt the old neurosurgical principle of increasing the patient's tolerance to cerebral anoxia by

daily carotid compressions. In this way it is possible, after a certain number of days, to arrive at a point where he can stand 10 minutes of bilateral carotid compression without symptoms. Over the past 2 years this method has been adopted, and all our patients are now prepared during the preoperative period by daily manual carotid compressions. They are not operated upon unless they can stand manual bilateral compressions of the carotid arteries for periods of 5 minutes without symptoms. This tolerance allows us, during surgery, to have the carotid vessels compressed in the neck by the anesthetist for a maximum period of 2 minutes during the manipulations of the auricle, during the application of the forceps at the base of the auricle, during the introduction of the finger, and finally during manipulations at the mitral opening itself. Carotid compressions are applied intermittently during these maneuvers, and it is extremely rare for the patient to have to withstand compressions of the carotid beyond a period of 1½ minutes at a time. This technique has been used in 75 consecutive patients and cerebral embolization has been encountered on 4 occasions. Only in 1 case has it been fatal; the 3 other patients have recovered fully. Comparing these results to the results of cerebral embolization in 5 of 50 cases previous to that time, when 4 were fatal and 1 patient recovered only 50 per cent of function, it is our impression that this technique is useful in protecting against this most dangerous of complications. We do not believe that this technique *prevents* the cerebral embolization on the table but rather that, because of the increased tolerance to cerebral anoxia, the damages resulting from cerebral emboli are minimized.

Fracture versus instrumental section. A study of Table I shows the number of times the commissures have been sectioned instrumentally, fractured digitally, or enlarged by the combined method associating the knife and the finger. In many cases this combined procedure has consisted of a completion of the fracture by the knife. Forty-three

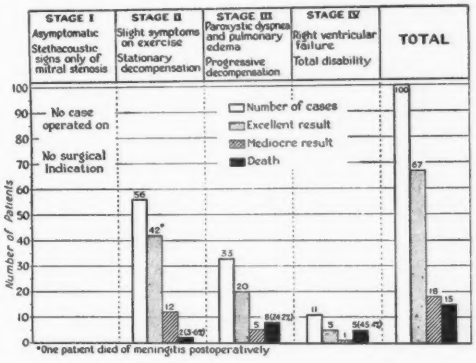

FIG. 1. Results in 100 consecutive cases of mitral commissurotomy. Follow-up periods of from 6 months to 4½ years. No case lost to follow-up.

per cent of the patients in our series have undergone fracture alone. It is interesting to note that in 7 of these patients digital fracture alone was possible though there were calcifications. In these 7 patients it was observed that the calcifications were present along the myocardial border of the leaflets and that the free edges of the leaflets as well as the commissures demonstrated very little calcification or calcifications sufficiently fragile to stand digital fracture easily. The combined technique (for a total of 40 per cent) represents for the most part an instrumental section to complete enlargement by digital fracture. The first 14 patients operated upon underwent instrumental section alone without attempt at fracture, as in those days the original technique, as it was established by Bailey, was followed implicitly.

Point of auricular entry. An important observation has been that the point of origin of the auricular appendage in many cases is narrow, though the auricle itself might be large with an irregular edge, giving the appearance of a cockscomb. This narrow point of origin has been encountered in more than 25 per cent of cases. By introducing the finger alone it is possible in all cases, by constant nonbrutal pressure, to dilate the point of implantation without tearing the wall of the atrium itself. It was only after

attempting to enter brutally, with the knife armed on the finger, in the first 14 patients and after having occasioned a few atrial tears by this brutal introduction, that this conclusion was reached. With deliberate but constant pressure of the finger it is possible in all cases to introduce the finger sufficiently far to do the digital fracture. If the knife has to be introduced subsequently it is quite easy to pull the finger back as far as the terminal phalanx and slide the instrument along the volar aspect of the exploring finger. No special technique to hold the knife attached to the finger is required if one uses exclusively a guillotine type of commissurotome. Nevertheless, when the knife must be used, the amount of hemorrhage between the finger and the instrument itself is necessarily larger.

Ideal mitral opening. We do not believe that it is necessary in all cases to obtain the maximum opening possible. We have on occasion intentionally limited it to a fracture of the lateral commissure alone, in this way obtaining an opening to approximately 2.5 centimeters. It seems impossible to establish rules for the opening to be obtained, as it is only during the operation, with the surgical finger exploring the mitral valve and in consultation with the cardiologist who has had the advantage of appreciating the myocardial reserve and the state of the other valves, that it is possible in individual cases to decide how far the mitral opening should be enlarged without producing mitral regurgitation. In cases in which it is impossible for the exploring finger to locate the medial commissure by following the intraventricular pillars on the medial aspect of the ventricle, as described by Rusted and associates, it is much better to limit the fracture or the section to the lateral commissure with a resultant opening to 2 or 2.5 centimeters than to attempt to fracture or cut on this side thereby producing serious regurgitation, most often fatal, as we have experienced on 3 occasions.

Pressures in the left atrium have been registered in 85 per cent of the cases and have demonstrated immediate fall to approximately 50 per cent of the previous value, though the fall in pressure appears not to be the result of the enlargement of the opening obtained as much as the constitution of the mitral leaflets themselves. When the mitral leaflets are thickened they do not always function completely, even following an adequate commissurotomy, and in these cases the fall in pressure will be less marked. On the other hand, according to the cardiologists who have followed these patients, patients with a limited enlargement of the orifice and with a drop in pressure of 50 per cent seem to obtain as good results as those who have had a much more marked enlargement.

CONCLUSIONS

1. The term of commissurotomy to indicate surgical enlargement of the mitral opening is to be preferred to the term of valvulotomy, valvotomy, or valvuloplasty.

2. The surgical results in 100 consecutive cases are presented.

3. Technical surgical considerations are discussed and it is proposed that: (a) Daily preoperative carotid compressions should be practiced to a point of maximum tolerance of 5 minutes without symptoms before operation. (b) Digital fracture is sufficient in 43 per cent of cases. The use of the commissurotomy knife seems to be reserved most often to complete a fracture. (c) The narrow point of origin of the auricular appendage can be dilated by steady pressure with the finger without fear of atrial tear. (d) It does not appear necessary to obtain a very large opening of the mitral valve in order to secure both subjective and objective relief and to reduce the intra-atrial pressures by 50 per cent.

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SPINAL ANALGESIA WITH PIRIDOCAINE HYDROCHLORIDE FOR CESAREAN AND VAGINAL DELIVERIES

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SPINAL ANESTHESIA for obstetric procedures has been the preferred method of the senior author (B. A. G.) since 1939 (5) and of the junior author since 1946. We have used procaine, pontocaine, or nupercaine in over 700 cesarean sections and over 7,000 vaginal deliveries without a death or major neurologic complication. Nevertheless, as a result of several encouraging reports on the value of piridocaine hydrochloride,[1] a trial of the drug was justified.

Spinal anesthesia with piridocaine hydrochloride was first reported by Finer and Rovenstine in 1947. They were impressed with the insignificant degree of motor paralysis during extensive analgesia obtained with 25 milligrams of the drug in 5 per cent glucose. This modality of anesthesia has been favorably appraised by Rovenstine, Barnes and Hapke, Conner and Dripps, and De Vivo in a total of 573 vaginal deliveries. Its usefulness in cesarean section, however, has not been determined, since it was employed by Finer and Rovenstine for only 27 sections and by Roman and Adriani for 5 patients.

Spinal analgesia without thoracolumbar motor paralysis is especially valuable to the parturient. She is exposed to anesthetic hazards associated with a full stomach, marked obesity, and an extremely large intra-abdominal tumor. She is also likely to develop excessively high levels of anesthesia as a consequence of uterine contractions and increased intra-abdominal pressure augmenting the cephalad movement of subarachnoid anesthetic agents. The best safeguard against these dangers is retention of voluntary muscular control of the abdominal wall regardless of the height of analgesia. Furthermore, profound abdominal motor paralysis is unnecessary in vaginal or abdominal delivery. Even an extraperitoneal cesarean section requires only the moderate and voluntarily controllable relaxation produced by blockade of the sensory limb of the spinal reflex arcs in the thoracolumbar area.

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[1]Piridocaine hydrochloride is beta—(2-piperidyl)—ethyl ortho—aminobenzoate hydrochloride. It occurs as a white, crystalline, odorless, nonhygroscopic powder which is readily soluble in spinal fluid in 2.0 per cent concentration. Aqueous solutions show a *p*H range of 6.2 to 6.8. Alkaline residues in syringes and needles must be avoided or removed to prevent precipitation of the free base. Piridocaine hydrochloride, marketed as lucaine hydrochloride, withstands autoclaving at 15 pounds pressure (120° C.) for 20 minutes. The specific gravity of a 1 per cent solution in 5 per cent glucose is approximately 1.020.

METHOD AND MATERIAL

During the past 4 years we have extensively tested spinal analgesia with piridocaine in several thousand patients for a wide variety of procedures in surgery and obstetrics (7). It was applied to 3,625 consecutive suitable parturients. The drug was used under conditions which govern our practice of obstetric spinal anesthesia, viz.:

1. Contraindications to spinal anesthesia hold for any drug or method.

2. The single dose technique is strongly preferred. Continuous spinal and epidural methods are more traumatic, cumbersome, time-consuming, and unreliable. They are more frequently associated with neurologic complications, even in the hands of experts. We reserve these special methods for exceptional indications (5).

3. Spinal analgesia for either vaginal or abdominal delivery requires the same technique and care; in either case analgesia should rise to the ninth thoracic dermatome.

4. Arterial hypotension during obstetric spinal analgesia does not depend on the

technique or drug. In full term patients hypotension is equally common and severe with single dose or continuous spinal analgesia or caudal or lumbar epidural anesthesia, when all other relevant factors are equal. The marked susceptibility to hypotension characteristic of full term patients in the supine position depends on mechanical interference with blood flow through the inferior vena cava which is compressed by an enlarged uterus in the supine patient. Even without anesthesia, retardation of blood flow in the lower extremities and pooling of blood in the abdomen and pelvis tend to occur in supine full term patients. This circulatory abnormality is aggravated by spinal or epidural anesthesia because the concomitant sympathetic block in the lower extremities reduces venous tone, an important component of the *vis a tergo* which is necessary to maintain an adequate venous return in the face of compression of the inferior vena cava.

5. Relief of labor pain may start when delivery is expected within 3 hours, provided obstetric conditions indicate that analgesia will not interfere with the progress of labor (8). The duration of spinal analgesia must be governed by expert evaluation of the expected progress of labor and mechanics of delivery. Variations in the duration of analgesia up to 3 hours should be obtained by changes in the composition of the anesthetic solution.

TECHNIQUE

For either abdominal or vaginal delivery the desired level of analgesia is the ninth thoracic dermatome. A vasopressor drug is injected 10 minutes before anesthesia in all but hypertensive patients. It is omitted when an infusion is in situ to allow intravenous injection of a vasopressor drug if necessary. The dose of piridocaine hydrochloride is 25 to 30 milligrams. The solvent is 2.5 to 3 cubic centimeters of 5 to 10 per cent glucose. Lumbar puncture may be performed in the second to fifth interspace, with the patient sitting or horizontal. After injection the patient assumes the supine horizontal position, with the head flexed. These factors provide effective analgesia for a cesarean section requiring 1 hour or for labor and vaginal delivery within 2 hours. When prolonged analgesia is desired, ephedrine sulfate, 1 cubic centimeter containing 50 milligrams, or epinephrine hydrochloride, 0.6 cubic centimeter of 1:1000 solution is substituted for an equal volume of the glucose solvent. Ephedrine and epinephrine extend analgesia for cesarean section by 30 and 60 minutes respectively, for labor and vaginal delivery by 60 and 120 minutes, respectively. The intrathecal use of vasoconstrictors does not potentiate motor paralysis in the thoracolumbar muscles.

Analgesia begins a minute or two more slowly than with procaine but is adequate for surgery in 5 minutes. Stabilization of analgesia is not complete for 15 minutes; a vasopressor drug in the analgesic solution delays fixation for another 10 minutes.

RESULTS

We have utilized spinal analgesia with piridocaine in 225 patients for cesarean section and 3,400 patients for labor and vaginal delivery. Analgesia is promptly and reliably obtained while a significant degree of motor power remains in the thoracolumbar zones. Regardless of the cephalad level of anesthesia, the patient can bear down forcefully when requested, cough vigorously, breathe normally, and, finally, assist in moving herself to and from the stretcher and operating table and in changing her position in bed. Incidentally, the act of vomiting retains the vigor of its abdominal muscular component so that it is as effective a force of labor as bearing down. Numbness and paresthesia are not so intense as to be distressing.

Failure to obtain analgesia occurred in 6 cases (0.16 per cent) and was apparently due to errors in technique. No death or serious neurologic complication has been attributable to the method or drug. Spinal headache occurred in 15 patients (0.4 per cent); the low incidence is credited, not to the

drug, but to the use of fine gauge needles for lumbar puncture and special effort to hydrate patients (6, 9).

SUMMARY AND CONCLUSION

On the basis of a completely satisfactory experience with 3,400 vaginal deliveries and 225 cesarean sections, we recommend the use of piridocaine hydrochloride by single dose, subarachnoid injection of 25 to 30 milligrams in 5 to 10 per cent glucose, with the addition of ephedrine or epinephrine when indicated. This technique promptly and reliably provides effective analgesia and pelvic muscular relaxation yet permits the retention of a significant degree of muscular control in the thoracolumbar area and lower extremities—features which are especially valuable in obstetrics.

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PARENTERAL TRYPSIN: ITS EFFECT ON EXPERIMENTAL THROMBOTIC AND INFLAMMATORY CONDITIONS

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PREPARATION of the enzyme trypsin in purified crystalline form has led to laboratory and clinical trials of its parenteral administration. Tagnon in 1945 reported that trypsin administered intravenously to laboratory animals gave rise to shock, to death from massive intravascular clotting when injected rapidly, and to an anticoagulant effect when given in sublethal doses. His findings were not such as to encourage clinical application.

The subject was reopened in 1952 by Innerfield and his co-workers who published data which suggested that Tagnon may have overestimated the toxicity of intravenous trypsin (2, 3). They found that their rabbits and dogs could tolerate doses up to 100 milligrams per kilogram provided it was given by slow drip and noted, moreover, that the enzyme when given in these larger doses exerted a "significant, but variable, lytic effect" on experimental intravascular thrombi. Subsequently this group began to use the enzyme intravenously in selected clinical cases, and in 1953 they published details of a large series of patients so treated (1). They reported excellent results, which they ascribed partly to an intravascular thrombolytic effect and partly to what is described as a specific anti-inflammatory action.

Following these original papers there have been a number of conflicting reports on the supposed thrombolytic effect of parenteral trypsin. Laufman and Roach were unable to confirm intravascular dissolution of clots with any dosage, although later they reported lysis of experimental pulmonary emboli in animals which had been pretreated with trypsin, then given a further dose after establishment of the emboli (6). Recently Taylor, Overman, and Wright on the basis of careful laboratory study have come to the conclusion that doses of trypsin large enough to affect the clotting mechanism of rabbits are dangerous on account of intravascular clotting, hemorrhages into the tissues, and focal necrosis, and that, furthermore, no intravenous dose of trypsin has any therapeutic effect whatever on experimental intravascular thrombi. They believe that trypsin "should not be distributed for general use at this time."

The revolutionary significance of a drug which would allow safe, controlled intravascular thrombolysis is self-evident, but it would appear that earlier claims made for trypsin in this regard have not been substantiated. Clinical reports of therapeutic benefit seem to be predicated more on an anti-inflammatory effect, and a new preparation for intramuscular administration is said to produce marked diminution in inflammatory reactions without the possible dangers associated with intravenous administration. The purpose of our project was to determine whether lysis of experimental intravascular thrombi could be achieved by parenteral trypsin, whether there were any dangers associated with the method, and finally, whether any anti-inflammatory effect could be demonstrated in animals under carefully controlled conditions.

EFFECT ON THROMBI

Technique of experiment. The enzyme was tested on standard intravascular clot preparations in a series of mongrel dogs. Each experiment consisted of three stages.

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TABLE I.—DOSAGE AND TOXICITY OF INTRAVENOUS TRYPSIN IN 19 COMPLETED EXPERIMENTS

No. of dogs	*Dose of trypsin, mgm./kgm.*	*Survived*	*Alive but moribund at 24 hours*	*Died within 24 hours*
6	75	1*	1	4
7	50	4	1	2
6	30	6	0	0

*Owing to leakage into the tissues, this survivor failed to receive the full dose of 75 mgm./kgm.

TABLE II.—DETAILS OF 4 DEATHS OCCURRING DURING TRYPSIN ADMINISTRATION

Series No.	*Total dose at death, mgm./kgm.*	*Time of administration, hrs.*	*min.*	*Cause*
7	37	2	12	Trypsin shock
8	15	1	30	Massive intravascular clotting
11	4		35	Undetermined—possibly anesthetic
15	75	2	30	Trypsin shock

Stage I. Standard clot preparation.—We adopted independently a technique differing only in detail from that described by Laufman and Roach.

A segment of upper femoral vein was exposed in each thigh and the central end narrowed by means of a ligature to about one-half of its original diameter. The segment was then occluded temporarily at each end by soft rubber bands, and 0.2 to 0.4 milliliter of dilute thrombin solution[1] was injected into it via a small tributary which was subsequently ligated. The occluding bands were left in place for at least 15 minutes, the distal one being removed a few minutes before the proximal. We have found this a simple and reliable method of producing experimental thrombosis without causing mechanical or chemical damage to the intima of the vessel.

Stage II. Administration of trypsin.—Approximately 24 hours after stage I the wounds were reopened and the presence of clot verified. Digital palpation was found to be an unreliable method of detecting thrombosis unless carried out so vigorously as to risk breaking up the clot, and the most consistently satisfactory indication was obtained by raising the vein gently on the beak of a curved hemostat. A patent vein promptly emptied where it crossed the hemostat, while a thrombosed one retained its shape and turgor.

The segment on one side was then excised as a control and refrigerated, and the dose of trypsin (enzar)[2] was given directly into the inferior vena cava via a polyethylene catheter inserted into the stump of the excised femoral vein. The calculated dose of trypsin was dissolved in a convenient volume of normal saline (usually 100 to 300 c.c.) and given by slow drip. A continuous blood pressure record was made in every case, and the rate of administration was determined largely by the presence or absence of hypotensive response.

In the average case a rate of approximately 2 milligrams per minute was well tolerated. At a dilution of 2 milligrams per cubic centimeter, this represents roughly 15 to 20 drops per minute. The optimum rate varied from dog to dog, however, and even from time to time in the same dog. A frequent finding was that the drip had to be very slow for the first few minutes, but could be speeded up as the animal settled down to the drug. Later, as toxic doses were approached, the infusion had to be slowed progressively. There were several exceptions to the rate of dosage mentioned. One animal tolerated 13.5 milligrams per minute without hypotension, while another went into moderate shock with only 0.9 milligram per minute.

Stage III. Evaluation.—Twenty-four hours later in survivors, and as soon as possible after death in nonsurvivors, the remaining thrombosed segment was excised and compared with the first, with particular reference to appearance, consistency, and adherence. At this stage, in most cases, the animals were sacrificed and autopsy performed, although some were allowed to survive for further varying periods.

Parallel in vitro experiment. It could be argued that the protocol given might fail to provide a fair test of the efficacy of intravenous trypsin. Dissection and manipulation

[1]Thrombin 1,000 units dissolved in 5 milliliters of normal saline solution.

[2]Measured as "milligrams of tryptic activity" (1 mgm. of tryptic activity = 1,000 trypsin units).

of the femoral vein might be postulated to cause spasm of, or actual damage to, its tributaries, and so prevent adequate access of the circulating enzyme to the intravascular clot. To meet this objection, a parallel experiment was carried out in vitro. Blood drawn from each animal immediately after the infusion of trypsin was added to a test tube containing a clot formed of the same animal's pre-experiment blood. The tube and contents were then incubated for 24 hours at 38 degrees C. A second similar clot was incubated by itself as a control. Clots were assessed at 24 hours for size, appearance, and consistency.

Results. Our experience with the toxicity of intravenously administered trypsin in 19 completed experiments is summarized in Table I. It can be seen that our upper limit of safe dosage is less than 50 milligrams per kilogram—under half of that found by Innerfield and his group. Moreover, there were 4 operative deaths, detailed in Table II, 3 of which occurred with doses of trypsin ostensibly within the safe limit. As indicated earlier, and as noted by Innerfield and associates (2, 3) and Tagnon, the rate of delivery is critical. Inadvertent speeding up of the infusion for a few minutes can cause severe and even fatal reactions not reflected by the total dosage or over-all rate of administration. Technical difficulties of this nature are thought to account for 2 of the operative deaths and must represent at least a potential hazard in clinical administration.

Types of toxic effect. There appeared to be three main dangers associated with intravenous trypsin administration.

1. Trypsin shock.—Rapid intravenous infusion of a small quantity of trypsin causes a sharp drop in blood pressure in the normal animal. In the early stages of an experiment such an episode of hypotension could be reversed quite quickly by slowing the drip. Later in the course of the infusion, however, increasing refractoriness of this spontaneous recovery became manifest. With large doses, the end result was an inexorable decline in blood pressure to shock levels, no matter how slow the delivery. On the theory that this type of shock may be due to histamine release, intravenous benadryl was given in some cases of the series. The results, however, were equivocal.

TABLE III.—PER CENT INCREASE IN PAW DIAMETER FOLLOWING PLANTAR INJECTION OF 3 PER CENT DEXTRAN

Experiment	*Time since dextran injection, hrs.*	*Cortisone treated, per cent*		*Trypsin treated, per cent*		*Control, per cent*	
		1	2	3	4	5	6
I	½	90	95	84	81	78	63
	1	73	85	73	72	64	53
	2	73	70	61	62	62	54
	3	54	64	63	61	62	46
	4	42	57	60	56	53	48
	6	35	37	51	53	51	49
	8	24	27	51	50	43	32
II	½	85	106	107	85	101	92
	1	71	86	93	87	91	83
	2	57	67	75	74	78	94
	3	61	81	81	74	94	83
	4	60	59	77	71	86	75
	6	34	44	63	49	61	52
	8	16	31	51	37	57	40
III	½	76	101	88	99	101	102
	1	68	76	76	94	85	195
	2	56	76	71	86	78	88
	3	54	52	77	83	76	99
	4	46	44	77	84	76	85
	6	27	24	55	78	57	70
	8	16	16	52	79	44	51

2. Massive intravascular thrombosis.—The immediate effect of the addition of trypsin to normal blood is to hasten coagulation. Massive intravascular clotting as noted by Tagnon was found at immediate autopsy in 1 of our 4 operative fatalities. This would seem to be a significant risk, even with small doses of trypsin, if the administration is inadvertently allowed to become too rapid.

3. Uncontrolled anticoagulant effect.—Marked prolongation of the clotting time was an invariable sequel to the intravenous infusion of trypsin in these doses. This effect appears to result from destruction of the main factors of the clotting cycle. The operative wounds showed a persistent bleeding tendency, and in 12 of the autopsies scattered internal hemorrhages of varying severity were found. In at least 1, this was believed the main cause of death.

In vivo effect. In no case was there any appreciable effect on the intravascular thrombi. In 4 cases in the series the clot dis-

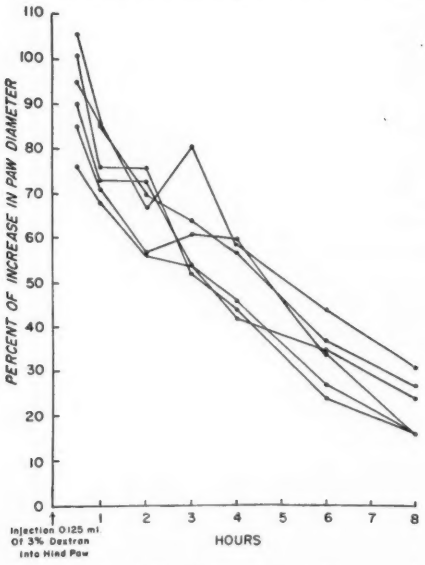

FIG. 1. Graph showing per cent of increase in paw diameter of cortisone-treated animals.

appeared from one or both sides. In each case, however, this preceded the trypsin administration, and autopsy subsequently showed emboli in the lungs of all these animals. This confirms the observations of Laufman and Roach and shows the ease with which experimental clots may migrate in spite of a narrowing ligature at the proximal end of the thrombosed segment. These findings indicate how cautious one must be in accepting disappearance of clot from its original site as evidence of lysis.

In vitro effect. In no instance did the test clots show any difference in size, appearance, or consistency from the controls.

In most cases, blood drawn from the animal following the trypsin infusion would not coagulate. In a number of instances, however, a fragile, delayed clot formed, and on 2 occasions this underwent lysis on incubation. In other instances, however, previously fluid blood actually coagulated during incubation, indicating that any lytic action must have been weak and inconstant.

Microscopic appearances. Histologic examination was not carried out routinely, and indeed some technical difficulty was experienced in preparing good sections of these friable clots. However, multiple sections were examined in 2 of the experiments. No appreciable difference was noted between the control and the trypsin specimens.

EFFECT ON INFLAMMATORY LESIONS

The belief that parenteral trypsin exerts an antiphlogistic effect is based largely on clinical series and there are few laboratory studies on record. Martin, Brendel, and Beiler, using the technique of egg-white injection into the hind paw of the rat, report a measurable anti-inflammatory effect from subcutaneous injections of trypsin. This finding was obtained both in intact and in hypophysectomized animals.

Laboratory experiments using animals with intact adrenals are of questionable value, however, because of the unpredictable action of the animals' own endogenous cortisone. For this reason we have studied the effect of intramuscular trypsin on experimental inflammatory lesions in bilaterally adrenalectomized rats. Strictly parallel control studies were performed by using equal numbers of untreated and of cortisone-treated animals. In this way it was possible to compare the effect of trypsin both with the untreated baseline and with the known antiphlogistic action of cortisone.

The technique employed was similar to that used by Martin, Brendel, and Beiler, except that dextran was used as an irritant, and serial measurements were taken instead of weighing the amputated foot. Preliminary experiments were carried out on several dozen rats to gain proficiency and to establish optimum technique. The following is a rather detailed account of our method of procedure.

Immature white rats of the Sprague-Dawley strain weighing 60 to 100 grams were used. Bilateral adrenalectomy under intraperitoneal pentobarbital anesthesia was performed a minimum of 48 hours prior to the observations. Following adrenalectomy the animals were maintained at an equable

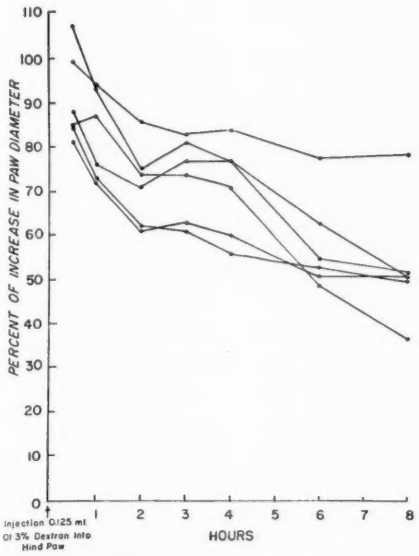

FIG. 2. Graph showing per cent of increase in paw diameter of trypsin-treated animals.

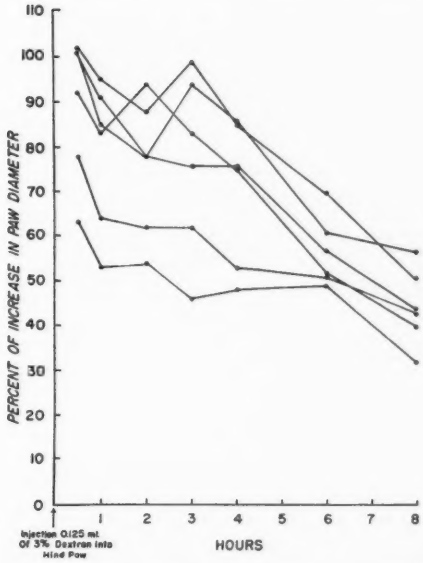

FIG. 3. Graph showing per cent of increase in paw diameter of untreated control animals.

temperature and were given 0.9 per cent saline in lieu of drinking water. Experiments were carried out on groups of 6 similarly sized animals at a time, 2 being cortisone treated, 2 trypsin treated, and 2 untreated. Cortisone was administered in the form of the acetate suspension, 2.5 milligrams being injected subcutaneously 48 hours, 24 hours, and ½ hour prior to the observations. Intramuscular trypsin (parenzyme) was administered in doses of 0.5 milligram at the same time intervals as the cortisone, and the manufacturer's instructions regarding the use of dry syringes were followed carefully. Since 5 milligrams of this preparation of trypsin are said to constitute a significant dose in the adult human, it was thought that rats so treated could be regarded as adequately saturated with the drug. An injection of 0.125 cubic centimeter of 3 per cent dextran[1] was placed under the plantar fascia of the left hind paw, using a 1 milliliter insulin syringe fitted with a 26 gauge needle. The thickness of the paw was measured with Vernier scale calipers from the plantar to the dorsal aspect at the level of the distal end of the first (medial) pad. The average of three measurements was taken at each observation, and if the range of variation was greater than 0.4 millimeter, the figures were discarded and the measurements repeated. In fact, the range was only very rarely as high as 0.4 millimeter. Measurements were made (by the same observer) immediately before the dextran injection and at intervals of ½, 1, 2, 3, 4, 6, and 8 hours thereafter.

Results. After establishment of the technique, observations were made on a consecutive series of 18 rats. In each case the first measurement prior to the dextran injection, was taken as the baseline, and the remaining figures were expressed as percentage increase in paw thickness. Usually the paw showed maximum swelling, up to double its normal size, at ½ hour, and thereafter shrank slowly over the ensuing period of the experiment. Anti-inflammatory activity could be demonstrated graphically by the steepness of this decline in paw size and by

[1]Six per cent flavolex diluted with an equal volume of distilled water.

the closeness of the final readings to the baseline compared with the controls.

The results are detailed in Table III and shown graphically in Figure 1. The latter demonstrates clearly the marked and consistent anti-inflammatory effect of cortisone indicated by the steep fall of paw thickness to low levels. No such trend is seen in the trypsin-treated series (Fig. 2), which is not notably different from the controls (Fig. 3). It must be concluded, therefore, that under the conditions of this experiment, parenteral trypsin cannot be shown to have any action on the experimental inflammatory process.

DISCUSSION AND CONCLUSIONS

In our series the only evidence for any thrombolytic effect of parenteral trypsin was the occasional dissolution on incubation of the poorly formed clots which appeared in some of the specimens drawn after the trypsin infusion. This was an inconstant phenomenon, however, and well formed clots of pre-experiment blood could not be demonstrably altered in vitro by incubation with blood drawn from the same animals after the trypsin infusion. This is in accord with the results of Roach and Laufman, who were unable to achieve intravascular thrombolysis except in cases pretreated with trypsin.

Our failure to produce any significant alteration in experimental thrombi with doses of trypsin much above the limit of therapeutic applicability suggests that intravascular thrombolysis by this technique is unlikely ever to be practicable. In any event, the peculiar dangers associated with the method do not commend it for general use.

As regards the effect of trypsin on inflammatory conditions, it is unfortunate that so much of the published work is based upon clinical impressions in diseases of such notoriously unpredictable course as acute thrombophlebitis and rheumatoid arthritis. The experiments detailed above seem to indicate that trypsin does not have any significant intrinsic anti-inflammatory effect.

Of the two therapeutic benefits attributed to parenteral trypsin, then, one has been convincingly refuted and the other seems highly questionable. We agree with Wright and his colleagues that it is difficult at present to advance any justification for its continued clinical use.

SUMMARY

1. Intravenous trypsin in doses greater than 30 to 50 milligrams per kilogram was found to be highly dangerous in the dog due to: (a) trypsin shock, (b) massive intravascular coagulation, (c) production of marked and uncontrolled anticoagulant activity.

2. Doses of 30 to 75 milligrams per kilogram had no significant lytic effect on experimental femoral vein thrombi in the dog, or on test tube clots incubated with blood drawn following the trypsin infusion.

3. No measurable effect from the use of parenteral trypsin could be demonstrated on experimental inflammatory lesions in rats in which the effect of endogenous cortisone had been abolished by bilateral adrenalectomy. Under identical parallel conditions the anti-inflammatory effect of cortisone injections was well shown.

4. From this study and from other reports in the literature it would seem that there is little justification at present for the clinical employment of parenteral trypsin.

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REFLEX SYMPATHETIC DYSTROPHY

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THE NORMAL AND EXPECTED RESPONSE of an extremity to trauma, either accidental or surgical, is one of orderly return to functional and anatomic integrity and to circulatory homeostasis. This implies the following: healing of the traumatized wound, amelioration and subsidence of pain, return of normal vasomotor tone and circulatory dynamics, and gradual return of function consistent with the degree of dissolution of continuity of soft parts and bone. These processes are slow or rapid depending upon the extent of trauma, the nature and degree of injury to specific tissues, the presence or absence of infection, and the adequacy of therapy.

Not infrequently, however, these reparative processes are disordered and they develop along patterns of persistence of pain and prolonged dysfunction. This disorganization of response is, in our experience, completely unrelated to the extent or nature of the trauma and may occur despite competent treatment and in the absence of infection or general metabolic disturbances which might militate against prompt healing. Furthermore, it is difficult or impossible to foretell, *at the time of trauma*, in which direction the reparative processes will proceed. There are no immediate signs nor symptoms which indicate that trouble is ahead, nor is there any constant association between specific tissue injury and this disordered response.

This pattern has been given many names: major causalgia, minor causalgia, Sudeck's atrophy, posttraumatic pain syndrome, painful osteoporosis, traumatic edema, and reflex sympathetic dystrophy, among others. Actually, this multiplicity of names suggests a multiplicity of syndromes, each of different etiology, and with different course and behavior. This has been the general assumption almost since the first detailed descriptions of this entity appeared in the literature. Percival Potts, in the late eighteenth century, first described this pattern of response, and in 1813, Denmark described a case treated by amputation of the arm. In 1864, Weir Mitchell in this country, and Sir James Paget in England gave classical descriptions of the severest form, and the former coined the descriptive term causalgia, literally, a burning pain. In 1900, Sudeck described, as a separate entity, a less severe form characterized by atrophy and osteoporosis, since known as Sudeck's atrophy.

It is our concept that these syndromes are basically one in etiology, in clinical manifestations, and in response to therapy, but with definitely discernible variations in severity. We have encountered three distinct gradations of this syndrome, each with characteristic clinical manifestations and responses to therapy. The term reflex sympathetic dystrophy seems to us to be most satisfactory since it is both etiologically and clinically descriptive and its use avoids adding another term to the confused literature. Reflex sympathetic dystrophy may be defined as an excessive or abnormal response of an extremity to injury and is manifested by 4 constant characteristics: excessive and unduly prolonged pain, vasomotor disturbances, delayed functional recovery, and trophic changes. Diagnostically, all 4 of these must be present in greater or lesser degree of severity in order to classify a specific case as one of reflex sympathetic dystrophy.

As for etiology, the injury may be almost trivial, with no dissolution of continuity of skin or soft tissues, or it may be one of great magnitude. One of our severest cases followed a blow of only moderate severity to the dorsal metacarpophalangeal joint. Others have followed the division of small sensory

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nerves, such as the dorsal branch of the radial nerve or the infrapatellar nerve in the course of operative procedures or have followed operations of varying magnitude upon the muscles, tendons, or bony parts of an extremity during which no known serious trauma to major peripheral nerves occurred. In no patient in our series was there a partial or complete severance of a major mixed peripheral nerve. It appears to us that variations in the nature and extent of trauma are of only minor significance in etiology, assuming of course, that any injury must, of necessity, stimulate and injure nerve fibers, particularly sympathetic fibers. Of more significance, apparently, is the constitutional totality of the individual particularly in regard to the lability of the sympathetic responses, the extent and distribution of sympathetic nerve fibers, and the character, presence, or absence of the so-called nocifensor nerves of Head, which Bingham believes to be special afferent sympathetic nerves conducting pain stimuli. It is also probable that predetermined patterns of pain sensation and response, individual characteristics of cerebral integration of afferent pain impulses, and the nature of the so-called internuncial pool, described by DeNo and elaborated by Livingstone, are significant. There is no agreement concerning the exact pathogenesis, but it is certain that at some period shortly after trauma there is a wide spread of excitation in the central nervous system which activates and bombards central cell stations into a frenzy of activity. This results in hyperactivity of the sympathetic system as well as in increased activity of the other reflex mechanisms. We can only believe that, once initiated, this state is perpetuated by defects in central integration or response, and that, on the basis of clinical signs and of response to therapy, the sympathetic nervous system is inextricably involved.

CLINICAL ASPECTS

In order to obtain maximal response to specific therapy, we believe that rigid diagnostic criteria must be established and conformed to. Unless this concept is followed, adequate therapeutic measures may be delayed until irreparable damage has been done or, perhaps worse, patients suffering from other types of organic or functional disease of the extremities may be subjected to incorrect treatment. These criteria, all of which must be satisfied in each patient, are: pain, vasomotor disturbances, delayed return of function, and trophic changes. As mentioned previously, these may be present in varying degrees or one sign or symptom may be so severe as almost to obscure the others. Nevertheless, we believe all must be present to establish a diagnosis of reflex sympathetic dystrophy.

The time and character of onset of signs and symptoms vary. Within a few hours after trauma, pain may develop in a mild or severe form and may soon become unrelenting. In other patients, the onset is insidious over a period of days or weeks and is manifested first by vasomotor changes or delayed functional return. In general, careful observation and understanding attention to the complaints of the patient will enable the observer to detect early some aberration of response before a fully developed syndrome is manifested, and in these cases treatment will be most effective. It is important to remember that gross injury to major peripheral nerves is not essential and that minor and apparently inconsequential trauma may produce severe and permanent impairment.

The pain may be excruciating, burning, or knifelike and lancinating, or it may be dull, aching, or throbbing. It may be present at rest or may only be elicited by motion. It may be aggravated by slight emotional or physical stimuli, or it may be constant, unrelenting, and of equal intensity. The pain is usually diffuse and is almost never limited to one dermatome nor to a definite area of nerve distribution. Frequently there is radiation along the entire extremity, and in involvement of the upper extremity, the radiating area may include the shoulder and the base of the neck as in the so-called "shoul-

der-hand syndrome." Pain may be so severe as to dominate the clinical picture and when the other signs are minimal, the afflicted patient may be classified as a malingerer or neurotic. Yet, careful observation will in all cases piece the entire picture together.

The vasomotor changes may be severe or mild but are always present and indicate an aberration of sympathetic function. Two principal variations may be observed. In one, vasoconstriction predominates, and the skin of the extremity is cold, thin and glistening, and profusely perspiring. In the other type, vasodilatation predominates and the skin is warm, dry, and scaly. In the former some relief is obtained by warm applications, while in the latter, cold may be effective. This variation of vasomotor response is dependent upon the distribution and stimulation of either the sympathetic vasoconstrictor fibers or the sympathetic vasodilator fibers (3).

Trophic changes are also variable in extent and degree, but are almost specifically related to the duration of the process. Skin, subcutaneous tissue, muscle, joint structures, and bone are involved. Edema is commonly present early, and osteoporosis is present late in the course. These changes are undoubtedly related, first to the vasomotor disturbances, and secondly to the pain which causes voluntary immobilization of the involved extremity.

Tardy restitution of function is characteristic. In the early phases, the patient may resist motion with determination because of pain and may develop an almost diagnostic rigidity of the extremity, guarding it against even the slightest disturbance. Later, when trophic changes have occurred, function is disturbed by mechanical causes which may persist long after pain has been relieved by treatment. However, functional impairment of mild degree frequently may be the initial sign and severe pain occurs in these patients only after active or forceful motion has been instituted. More characteristically, minimal or delayed dysfunction appears to be distinctly secondary to pain and vasomotor disturbance at the onset, but with time this dysfunction obtrudes itself more and more into the clinical picture and may be the most disabling feature of reflex sympathetic dystrophy. Furthermore, delay in treatment may result in permanent dysfunction even after pain has disappeared completely and circulatory homeostasis has been restored. The dysfunction, not infrequently, may involve structures some distance removed from the site of the original injury.

CLASSIFICATION

Three distinct gradations of reflex sympathetic dystrophy may be clearly defined in terms of onset, intensity, and relative predominance of one group of symptoms over the others. The nature of the initiating trauma is rarely of value in classification since all gradations occur after either mild or severe injury.

Grade 1. Pain dominates the clinical picture in this group. The onset is usually within a few hours after injury but may be delayed occasionally for days and, rarely, for weeks. Pain is of maximal intensity, stabbing, lancinating, or burning, and not relieved by rest. It is aggravated by slight emotional or physical disturbances and, in fact, these afflicted patients appear to be hypersensitive to the slightest psychic trauma or environmental change. Vasomotor phenomena are also severe and may result from vasoconstriction or vasodilatation, as described previously. There is a fixed voluntary immobility of the involved extremity and the slightest motion is resisted. As a result, trophic changes of skin and subcutaneous tissue and eventually of muscles and bone appear. If relief of pain is not accomplished within a reasonable time, permanent functional impairment may result. We have seen grade 1 severity as a result of various types of trauma, frequently of a minor nature, such as a contusion or sprain or the division of a small sensory nerve.

Grade 2. This represents a milder form, slower in development and, as a result, of longer duration. Symptoms develop days or

TABLE I.—RESULTS OF TREATMENT OF REFLEX SYMPATHETIC DYSTROPHY IN 147 CASES, CLASSIFIED ACCORDING TO TYPE OF THERAPY AND GRADE OF SEVERITY

	Continuous procaine paravertebral ganglionic block			*Surgical sympathetic ganglionectomy**		
	Excellent	*Good*	*Poor*	*Excellent*	*Good*	*Poor*
Grade 1..	1	14	2	4	4	1
Grade 2..	25	25	4	6	5	—
Grade 3..	56	17	3	—	—	—
Total....	82	56	9	10	9	1

*All cases in this group received a trial of continuous procaine block and are included in that group.

weeks after trauma and build up in intensity. Pain is present but is rarely of the severe, lancinating, or burning type. It is dull and aching, definitely aggravated by motion and diffuse; the entire extremity may throb or ache. Motion, rather than psychic stimuli, is the aggravating factor and the patient seeks rest. Frequently the immobilization imposed by the patient is accentuated by rigid casings of plaster or other material applied by the physician. Vasomotor changes are always present but are mild and may, in the early phases, escape casual observation. Atrophy develops and easily detectable reduction in the circumference of the involved area soon becomes clinically apparent. Serial roentgenographic studies (and comparisons with the uninvolved extremity) show progressive osteoporosis. Coincident with atrophy and osteopororis, functional dystrophy appears, becomes pronounced, and may become permanent. Unfortunately, in a sense, the pain is mild and does not present an insistent demand for treatment. As in grade 1, the initiating trauma may be mild or severe and does not necessarily involve injury to major peripheral nerves.

Grade 3. This is the mildest form, the most common in our experience and the most frequently overlooked. These patients represent the border zone between normal response of an extremity to trauma and the more severe dystrophies just described. We have observed this variation most commonly as a sequela of surgical procedures on the extremities. The onset is early but insidious and may be manifested by the necessity for increased postoperative sedation beyond the ordinary requirements. The patient is reluctant to start active motion and resists passive motion. When the extremity has been immobilized by plaster bandages, it is frequently necessary to remove these because of pain and a sensation of undue pressure. Yet upon examination, the wound may be clean and healing, and no evidence of excessive pressure is observed. However, even at this early stage, vasomotor changes are present both objectively and subjectively. The part may be cold, clammy, and perspiring excessively, or it may be hot and dry. The patient experiences temperature changes limited to the extremity or to the local part, and mild burning pain is a frequent symptom. Local edema may be detected. Trophic changes are not present at this time, but will develop as symptoms persist. As in all patients suffering from reflex sympathetic dystrophy, impairment of function and trophic changes proceed concurrently.

TREATMENT AND RESULTS

The comprehensive treatment of patients with reflex sympathetic dystrophy demands prompt diagnosis, accurate classification, and early institution of specific therapy. Delay in diagnosis or treatment allows patterns of pain to become fixed and dysfunction and atrophy to become irreversible.

Specific therapy is a three-fold task. First, the patient must understand the nature of the disease, its organic basis, and the possibility of relief in order that co-operation may be obtained. Secondly, expert and patient guidance is required from the physical therapist to whom is entrusted the difficult task of aiding in the restoration of function as rapidly as subsidence of pain will allow. Thirdly, and most important, interruption of sympathetic outflow either by procaine ganglion block or by surgical sympathetic ganglionectomy must be accomplished. The former is best performed, we believe, by continuous procaine paravertebral ganglionic block by the method previously described by us (1). Surgical ganglionectomy is accomplished by transpleural removal of the sec-

ond, third, and fourth thoracic ganglia and occasionally the stellate ganglion for the upper extremity and extraperitoneal removal of the first, second, and third lumbar ganglia for the lower extremity. The choice of therapy is determined by the clinical classification of the grade of severity and by the initial responses to conservative therapy.

Grade 1. We believe that early *surgical* sympathetic interruption is necessary in patients with disease of this severity. While procaine block may afford temporary relief in some, it does not appear to be efficacious in preventing recurrence. We have instituted continuous paravertebral procaine blocks for periods of 7 to 21 days in 17 patients classified as of grade 1 severity. Of these, only 1 was completely relieved, 14 were relieved during the block but symptoms recurred after removing the paravertebral catheter, and in 2 patients the block failed to give relief. Nine patients in the latter two groups were subsequently subjected to surgical ganglionectomy (D.F.C.) with 1 failure, 4 good results (some residual functional impairment), and 4 excellent results (Table I).

Grade 2. With this grade of severity the early institution of continuous paravertebral procaine ganglion blocks may arrest the disease before functional impairment becomes severe or permanent. In our series, blocks were continued for 14 to 21 days in 54 patients. During this period, pain was relieved, normal circulation was restored, and function was improved in all but 4 patients. Twenty-five patients were completely relieved by blocks and required no further therapy. Twenty-five patients improved markedly during ganglionic blockade, but 9 of these suffered relapses at the termination of the blocks and the remainder showed some permanence of trophic changes and functional impairment despite relief of pain and restoration of circulatory dynamics to normal. As mentioned, there were 4 failures. Eleven patients (9 who suffered relapses and 2 of the failures) were subjected to surgical sympathectomy (D.F.C.). Of these, 6 had excellent results and 5 were completely relieved of pain but functional impairment and atrophy persisted, although to a lesser degree.

Grade 3. All of our patients in this group have been treated by continuous procaine ganglion block, for periods of 5 to 21 days. Surgery is rarely, if ever, indicated if a prompt diagnosis is made and early procaine sympathetic interruption is instituted. With this therapy, pain rapidly subsides, edema disappears, circulation becomes normal, and early motion is tolerated. We have now treated 76 patients in this group with only 3 failures (Table I). The latter were so classified because either no relief was obtained during blockade of the selected ganglia or because minor relapses occurred later to a degree that delayed rehabilitation.

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THE CYTOLOGIC DEMONSTRATION AND SIGNIFICANCE OF TUMOR CELLS IN THE MESENTERIC VENOUS BLOOD IN PATIENTS WITH COLORECTAL CARCINOMA

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THE TECHNICAL ADVANCES in the surgical treatment of colorectal carcinoma have not yet brought about commensurate improvement in curability. This disparity is based in part on the frequent development of hepatic metastases following resections of lesions that, from the pathologic standpoint, were considered to be "curable." Hepatic and other visceral metastases have been cited as the cause of death of nearly 50 per cent of the patients undergoing curative resection. This unfavorable turn of events undoubtedly results from the venous spread of the carcinoma.

It appeared to us that significant information concerning the venous spread of colorectal carcinoma might be obtained from a cytologic study of the blood of the major venous channels emanating from the neoplasm. The purpose of this investigation was to determine whether tumor cells were present in this blood, particularly in those lesions showing no histopathologic evidence of vascular extension.

MATERIAL AND METHOD

This study is based on 25 consecutive bowel resections for colorectal carcinoma. Fourteen were rectal carcinomas treated by abdominoperineal resection; 3 were cecal carcinomas treated by right colectomy; 4 were carcinomas of the sigmoid colon, 3 of the transverse colon, and 1 of the descending colon, all treated by wide resection. The procedures in each case were as follows: The abdominal cavity was entered, and before handling the tumor the operator ligated the arteries and veins in the most proximal portion of the regional mesentery (Fig. 1*A*). Venous collaterals were ligated to prevent the escape of the major portion of venous blood from the tumor area. In those instances of carcinoma of the rectum and of the sigmoid colon, the inferior mesenteric artery and vein were ligated at the inferior border of the third portion of the duodenum. In resections for carcinoma of the cecum, the ileocolic and right colic vessels were ligated at their origin at the duodenum. In carcinoma of the transverse colon, the midcolic vessels were ligated, together with the marginal vessels, at the proposed site of resection. Following ligation, the cancer-bearing segment of colon was mobilized in the usual manner with minimal handling of the neoplasm. When mobilization was complete, an occlusive silk tie was placed about the mesentery nearer the tumor (Fig. 1*B*), so that a column of blood was trapped between two ligatures.

On receiving the resected specimen in the laboratory, the isolated venous segment was immediately dissected free of the mesentery. Particular care was taken to avoid laceration of this structure, or incision of lymph nodes that in 1 instance were found along the course of the vein. The primary ligature was then removed from the end of the vein and the blood was emptied into a 50 cubic centimeter centrifuge tube. Through a No. 25 needle the vein was irrigated with saline solution until the return flow from the vein was clear. Usually 20 cubic centimeters of

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aline solution were required. The mixture f blood and perfusate was then centrifuged or 10 minutes and the supernatant fluid was decanted. A stained cell suspension was prepared from the sediment, utilizing toluidine blue in equine serum (equal parts of 1 per ent toluidine blue in 20 per cent alcohol nd equine serum) according to the method cently described by Hazard.

In addition to the cell suspension, 2 smears ere prepared and fixed in acetic alcohol (3 er cent glacial acetic acid in 95 per cent hyl alcohol). The smears were stained with G 6 and EA 50 as in the Papanicolaou ethod. A cell block was prepared by mixg an equal part of heparinized plasma with e remainder of the sediment and adding 4 rops of thrombin to each cubic centimeter total volume. The cell block was fixed in enker's fluid and processed in the usual anner with paraffin infiltration. Sections ere cut at 5 micron thicknesses from 3 levs of the cell block and then stained with ematoxylin, eosin, and methylene blue. The erfused segment of vein was excised, coiled, ixed in Zenker's fluid, and was processed in the usual manner with paraffin infiltration and was also sectioned at 3 levels.

The bowel was then opened longitudinally; the debris overlying the tumor was scraped away with a clean scalpel blade, and 2 direct smears were made from the neoplasm. The spreads were processed and stained in the same way as those prepared from the blood, but were fixed in different containers and stained separately, to eliminate the possibility of "contaminating" those smears made from the blood.

The resected segments of colon were fixed overnight in alcohol-formalin (90:10) and then sectioned at 3 millimeter intervals for

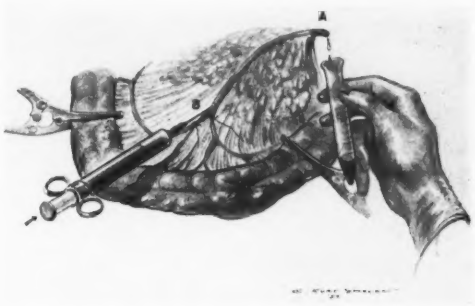


FIG. 1. Illustration demonstrating perfusion of vein. Primary ligature has been removed at *A* and perfusate is being collected in a centrifuge tube.

identification of lymph nodes and estimation of the degree of pericolic infiltration by tumor. An average of 3 blocks was taken from each tumor. Sections were stained with hematoxylin, eosin, and methylene blue, as well as by a combined Masson trichrome and Verhoeff elastic tissue stain.

As a control study for the cell types observed in the blood, the blood from 6 colonic resections for ulcerative colitis was similarly examined. In addition, the mesenteric veins from 2 normal colons obtained at necropsy were thoroughly washed and the perfusates examined.

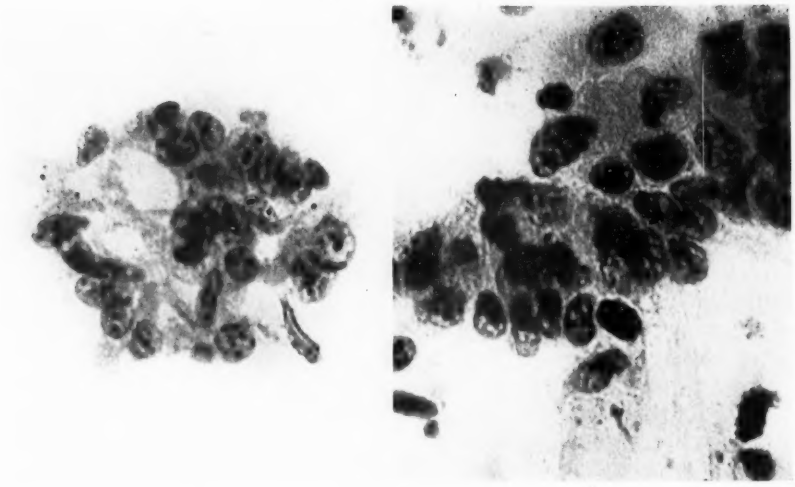
Cytologic criteria for identification of tumor cells in mesenteric blood. In the smears and suspensions of the blood, only those cells which were morphologically identical with those noted in the direct smear from the neoplasm were considered to be tumor cells. Two types of tumor cells were recognized. One type was characterized by its occurrence in groups and a round nucleus, the second type by its occurrence singly and having an ovoid nucleus. Both had prominent nucleoli and clumps of nuclear chromatin and relatively

TABLE I.—RELATION OF SITE OF TUMOR AND CYTOLOGIC FINDINGS

Site of lesion	*No. of cases*	*Positive cytologic findings*
Rectum	14	5
Sigmoid	4	0
Cecum	3	0
Descending colon	1	0
Transverse colon	3	3
Total	25	8

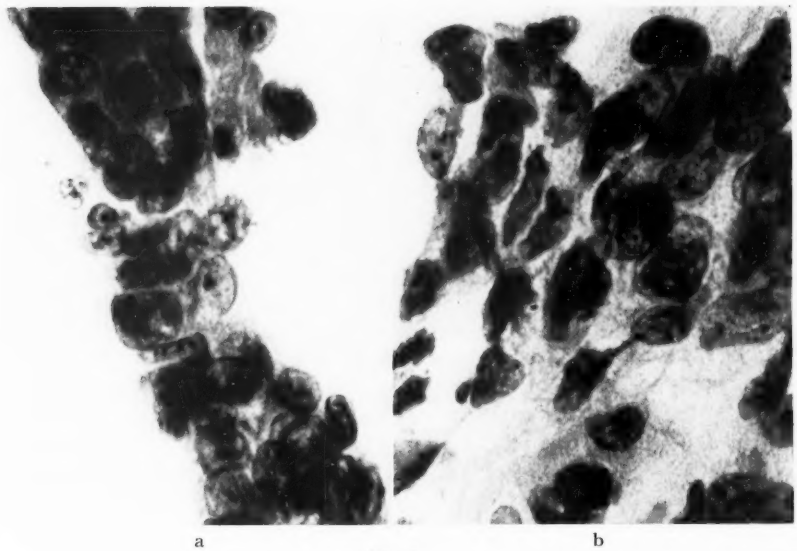
TABLE II.—CORRELATION OF DUKES' CLASSIFICATION OF CARCINOMA—HISTOPATHOLOGIC AND CYTOLOGIC EVIDENCE OF VENOUS EXTENSION

Dukes' classification of carcinoma	*No. of cases*	*No. of cases with evidence of venous extension*	
		Histopathologic	*Cytologic*
A	5	0	1
B	15	5	6
C	5	2	1
Total and per cent	25	7 (28%)	8 (32%)



a b

Fig. 2.

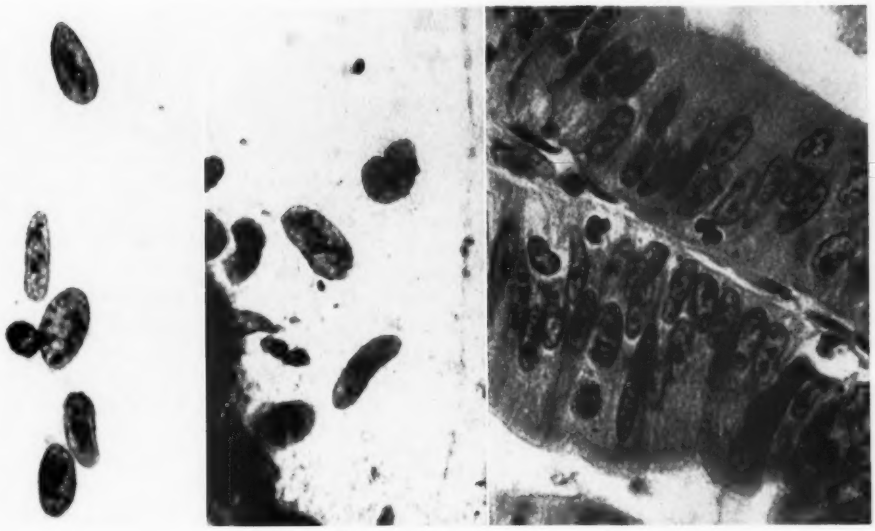


a b

Fig. 3.

FIG. 2. On the left, a, is a cluster of tumor cells recovered from the venous blood in the Dukes' A lesion (Papanicolaou smear, × 795). The cells are similar to those observed in the direct smear from the tumor as depicted in b (× 795).

FIG. 3. On the left, a, is a large cluster of tumor cells in a Papanicolaou smear prepared from the venous perfusate (× 795). The cells are similar to those noted in the direct smear of the tumor as shown in b (× 795).



a b c

FIG. 4. On the left, a, are ovoid tumor cells observed in the Papanicolaou smear made after venous perfusion. The cell cytoplasms are not apparent (× 795). This is also noted in the cells of the smear made directly from the tumor and shown in b (× 795). c, Similar cells observed in histologic preparation of the tumor after Zenker's fixation (hematoxylin and eosin, × 795).

scanty cytoplasm, resulting in an abnormal nuclear-cytoplasmic ratio (Figs. 2a, 3a, and 4a). Because of its fragility, the cytoplasm of cells of the second type were observed only in the suspensions, and their identification in smears depended entirely on the configuration and structure of the nucleus. The cytoplasmic fragility of these cells was similar to that observed in corresponding neoplastic cells in the direct tumor smears. In 1 instance, cells of the signet-ring type were observed in the smear from the blood. The neoplasm in this case was in part a signet-ring cell type.

The usual cellular elements of the blood obtained by perfusion were readily recognized. Endothelial cells were distinguished from the tumor cells by the regularity of the nuclear membrane, by the absence of prominent nucleoli, and by the clumping of chromatin (Fig. 5). Furthermore, these cells often had tapering, bipolar, cytoplasmic processes that apparently were less friable than those noted in tumor cells, since they were identified in the smears as well as in the suspensions.

Histopathologic criteria for judging vascular extension. The basis for judging vascular extension in histologic preparations was either the demonstration of the smooth muscle coat or of the elastica of the vessel. The smooth muscle coat often was observed in routinely stained preparations. However, in all instances verification of the presence of these structures was obtained by study of smooth muscle and elastic tissue stains before a venous tumor thrombus was identified.

RESULTS

Appraisal of cytologic technique. Consistent results in the identification of tumor cells were obtained both with the suspension and with the smear methods. In only 1 instance was the suspension positive and the smear negative. The converse was not observed. The cell blocks and the sections of the veins were negative in every instance. Tumor cells were identified in 8 (32 per cent) of the cases.

FIG 5. An endothelial cell is shown in center of the photomicrograph of a Papanicolaou smear made from a venous perfusate. The cytoplasmic processes of this cell are evident. Compare with cells in Figures 3 and 4. Other cellular elements of the blood are evident (× 795).

Relationship between positive cytologic finding and site of lesion. Table I shows the relationship between the incidence of positive findings and the sites of the lesions. Tumor cells were observed only in the blood of patients with carcinomas of the rectum and of the transverse colon; however, only a few lesions from other sites were studied.

Correlation of Dukes' classification with histopathologic and cytologic evidence of venous extension. Table II presents the results from the 25 cases classified according to Dukes' method. The presence or absence of venous extension as observed in the histologic sections, and the presence or absence of tumor cells in the smears is noted. In 1 of the 5 Dukes' A lesions (carcinoma limited to the muscular coats of the bowel) tumor cells were found in the perfusate, but none presented histopathologic evidence of venous extension. Cancer cells were identified by the cytologic technique in 6 of the 15 Dukes' B lesions (neoplasm extending into the pericolic fat); but only 5 lesions had evidence of venous extension by the conventional histologic methods. In the 5 Dukes' C lesions (characterized by lymph node metastases), tumor cells were observed only once by the cytologic technique, but twice in the histologic preparations. All of the Dukes' C lesions exhibited extension into the pericolic adipose tissue as well as lymph node metastases, and in 2, hepatic metastases were found at the time of operation.

Comparison of histologic and cytologic findings. In a comparison of the histologic and cytologic findings, of 7 lesions with histopathologic evidence of venous extension, 4 had tumor cells in the perfusates. However, of 18 lesions not demonstrating venous extension by histologic methods, tumor cells were found by the cytologic technique in 4 (22.2 per cent).

DISCUSSION

Jonescu, Knox, Marcus, Pool and Dunlop, Quensel, and Schleip have attempted to demonstrate tumor cells within the peripheral venous blood in experimental animals as well as in humans. The methods utilized, as well as the results, perhaps have adversely affected the significance of these studies. The difficulty in establishing the true identity of atypical cells within the blood has been emphasized by Pool and Dunlop. They found atypical cells in the peripheral blood of 17 of 40 patients having cancer, but were uncertain that these were cancer cells. These same authors mention obtaining blood from the mesenteric vein of 1 patient with carcinoma of the sigmoid colon, but did not report results of this study. We have not found any other record of the study of mesenteric venous blood in instances of colorectal carcinoma.

The use of a relatively small quantity of blood from a selected area within the portal circulation as performed in this study has minimized the objectionable feature of dilution attendant with the use of blood obtained by cardiac puncture or from the antecubital or other peripheral veins. Since only those cells that were morphologically iden-

ical with the epithelial cells of the direct mear from the tumor itself were considered s positive examples of cancer cells, there is asonable certainty that the atypical cells bserved within the blood in 32 per cent of e cases have been correctly interpreted as ing tumor cells. Further, the blood of the ntrol specimens did not reveal cells similar those considered to be tumor cells. The periority of the suspension and Papanicou smear methods over the cell block techque employed in other studies of the periphal blood for neoplastic cells is well demonated by this study.

Those cases with histopathologic evidence venous extension but negative cytologic dings are worthy of comment. Such an onsistency may be explained by the premis that the histopathologic evidence of veus extension does not necessarily imply bolization. Angioinvasive neoplasms in her regions of the body, particularly the capsulated angioinvasive carcinoma (angioinvasive adenoma) of the thyroid gland, do not consistently metastasize. The marked desmoplastic response observed in colorectal carcinoma, with coincident obliteration of venous structure, might also be a factor in accounting for this disparity between the histologic and cytologic observations.

Since tumor emboli are purportedly sporadic it would appear to be more than fortuitous that we observed such a supposedly inconstant phenomenon in one-third of the cases studied. The possibility that such embolization, especially in cases without histopathologic evidence of venous extension, results from operative manipulation is worthy of consideration. Such a possibility recently has been suggested by Cole and is implied in the studies of Bacon and Jackson. Much experimental evidence has accumulated which indicates that the spread of tumors is greatly enhanced by massage even in supposed premetastatic stages. However, actual proof that the tumor cells observed within the mesenteric venous blood in this study are the result of operative manipulation is not evident. Further studies have been planned in an attempt to resolve this problem.

The finding of tumor cells within the mesenteric venous blood strongly argues for the use of preliminary venous ligation in the surgical treatment of colorectal carcinoma. However, the possibility of tumor cells being shunted through small, intact venous channels must be considered. Whether preliminary venous ligation actually will improve the survival rate of patients having surgical treatment for colorectal carcinoma must await evaluation.

SUMMARY AND CONCLUSIONS

Tumor cells were recovered from the blood of the major mesenteric venous channels in 8 of 25 (32 per cent) cases of colorectal carcinoma by a perfusion technique. Only those cells that were morphologically identical with the epithelial cells observed in direct smears from the neoplasm were considered as positive examples of tumor cells. Such cells were found in 4 instances in which histopathologic evidence of venous extension was not observed. The presence of these cells in 1 of 5 lesions classified as Dukes' A offers an explanation for the malignant clinical course exhibited in the occasional patient with a lesion considered favorable.

The results of the cytologic technique were negative in 3 of 7 cases in which venous extension was observed by histologic methods. Such an inconsistency might well be explained by the premise that the presence of vascular tumor thrombi does not necessarily imply that embolization will result.

The correlation of the results of this study with those of previous experimental investigations concerning the venous spread of tumors raises the possibility that manipulation of the neoplasm may result in the venous dissemination of tumor cells. However, actual proof for such a contention is at present lacking. It would appear, nevertheless, that preliminary venous ligation is a logical procedure to avoid the possibility of the venous dissemination of tumor cells in patients with colorectal carcinoma.

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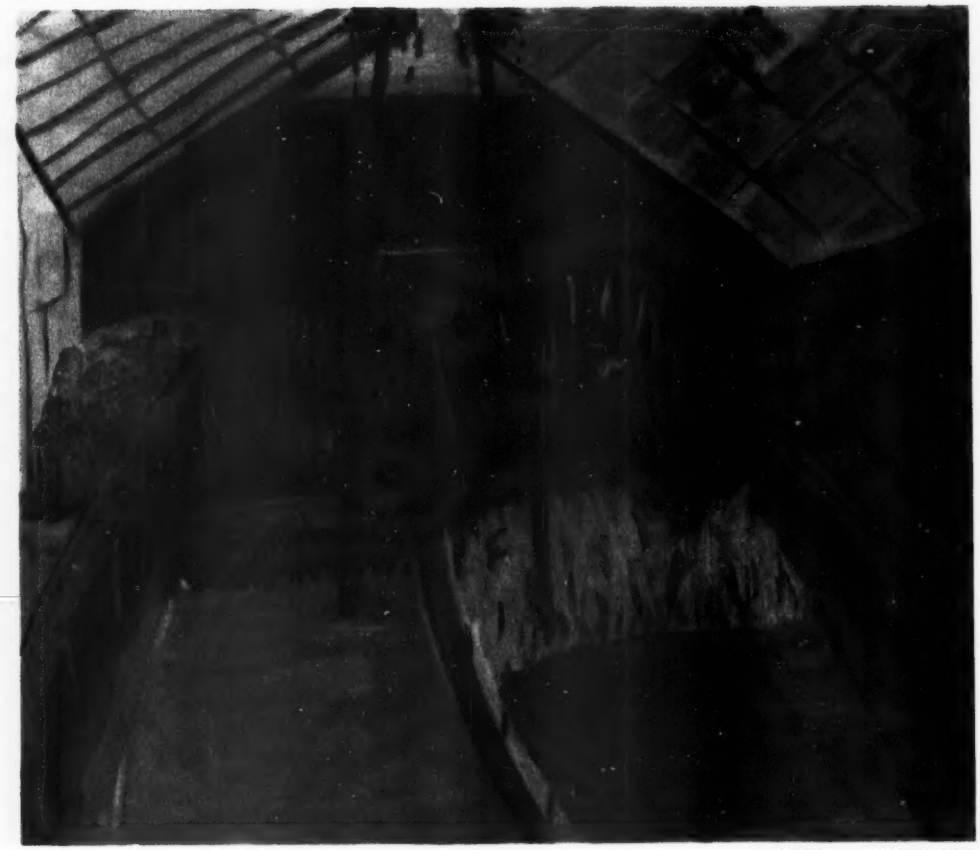

MICHAEL L. MASON, M.D.

The Greenhouse

EDITORIALS

A FIFTIETH ANNIVERSARY

UMNER L. KOCH, M.D., F.A.C.S., Chicago, Illinois

ANNIVERSARIES have long provided an opportunity for congratulations from friends and well wishers. Perhaps they should more often suggest a pause for soul searching as well—as to lost opportunities, as to misses and near-misses, as to failures to live up to high standards when energy slackened or aspirations dwindled.

In looking back over the past half century and recalling the original ideas of the founders of SURGERY, GYNECOLOGY AND OBSTETRICS, which Dr. Davis has presented elsewhere in this issue, we may ask ourselves if those ideas are still valid in this changing world, or if perhaps there should be some change of emphasis in the coming years. Notable changes have taken place in every branch of medical science in the past fifty years. One needs only to review the mortality statistics of life insurance companies to realize to what an extent diseases due to infections, both epidemic diseases and surgical infections, have been brought under control, and how other causes of death—cardiorenal and vascular diseases, cancer and trauma—have increased in relative importance.

As surgeons have made progress in new fields long considered impossible of approach, notably in the field of cardiovascular surgery, time honored surgical procedures of the ablation type are being replaced here and there by physicochemical therapeutic procedures. As has often been suggested it is entirely conceivable that in the next half century the center of activity of the surgeon will move from the operating room to the laboratories of physics and chemistry, and active surgical treatment will be concerned chiefly with congenital deformities and trauma.

Today significant changes in the social order also confront the surgeon. The constantly increasing life span is bringing new and difficult problems to the medical profession. It is a primary obligation of the surgeon to save life and relieve pain and suffering. If the concept of that obligation is enlarged to the point that life is saved or prolonged at the expense of a normal or nearly normal way of life one may sometimes question the wisdom of the surgeon's decision. One might ask, for example, if it is justifiable to carry out a massive resection of structures essential to one's well being for the sake of a few more months or years of life, and perhaps unhappy months as well. One might ask if it is justifiable to expend large quantities of precious blood, to preempt for long periods costly hospital facilities in anesthesia, operating room service, and skilled personnel in the hope of performing a miracle when the anticipated outcome actually was never in doubt. One might ask what it shall profit a man if he gain new arteries to his lower extremities while the slow but inexorable deterioration of his cerebral circulation goes on unchecked.

Although we can see only as through a glass darkly the many changes that lie ahead of the surgical profession in the coming years we cannot doubt that a forum for

studied surgical opinion and judgment, based on thoughtful observation and study, both experimental and clinical, can continue to serve as a guide and inspiration to workers far and near, and that the original ideas and ideals of the founders of SURGERY, GYNECOLOGY AND OBSTETRICS provide a structure upon which their successors can continue to build with the assurance that they are fulfilling their obligation to the surgical profession and to the public which it serves.

THE TREATMENT OF AORTIC ANEURYSMS

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THERE ARE few technical achievements in surgery more brilliant than the conquest of aortic aneurysms by excision of the involved segment and its replacement with a homologous graft. This did not come about with ease. Like so many advances in surgery, the method of its accomplishment lay for a long time written and recorded for all eyes to see before it was applied deliberately and successfully in an attack on this distressing malady, which by its very magnitude seemed to forestall thought of such aggressive action by surgeons. In 1907 Carrel had already successfully replaced segments of the aorta in dogs by homologous grafts, and he stated, "Homoplastic transplantations have been performed. For instance a segment of the aorta or the vena cava is extirpated and interposed between the cut ends of the aorta or vena cava of another animal. . . . The continuity of the vessel would very easily be reestablished by the biterminal transplantations of a vein or of an artery. After having extirpated an aneurysm it is possible to interpose between the cut ends of an artery a segment of the neighboring vein or of some other vein, the saphenous or the external jugular for instance." In 1913 Lexer of Jena successfully removed an aneurysm involving the iliac and femoral artery and replaced the vessel with a saphenous vein graft.

The original efforts go back, way back, to a time when the people of most of Europe were illiterate and did not record progress, when even those of the Mediterranean countries wrote and recorded little. In the second century there lived a Greek named Antyllus who advocated and, it is recorded, actually ligated the artery proximal and distal to the aneurysm and evacuated its contents. This is almost legendary because Antyllus' works are not extant and are only preserved by the writings of Oribasius who lived in the fourth century. It is to be noted that ligation of vessels is mentioned here for a cure of aneurysms but not for the control of hemorrhage, which the great Ambroïse Paré (1510–1590) made a standard surgical procedure. Time passed, centuries of it, and little was known and little was done to control aneurysms. Vesalius who published *De Fabrica Humani Corporis* in 1543 is credited with the first description of large aneurysms of the body cavities, for prior to him accurate intrinsic anatomy and pathology was little known. More time went by. Though the circulation of the blood was understood after Harvey published *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* in 1628, little reference was made to the treatment of aneurysms. It is true that Anel in 1710 employed proximal ligation for aneurysm and Brasdor (1721–1797) suggested distal ligation which was first performed by Wardrop in 1828. John Hunter (1728–1793) advocated ligating the artery some distance proximal to the aneurysm in normal tissue. At this stage, and even to the beginning of

this century, treatment of aneurysms was spoken of as if it were for aneurysms in general but it was applied usually to aneurysms of the periphery, and it is evident that the most common aneurysm to be treated was at the site of the popliteal artery. Moore introduced wiring in 1864. He used silver wires and the idea was to irritate the wall of the aneurysm and cause a clot. Endo-aneurysmorrhaphy was first performed in 1888 by a young surgeon who still lives. It was accomplished while operating upon a traumatic brachial aneurysm which "resisted proximal and distal ligation." This brilliant and lovable surgeon, Rudolph Matas, has endeared himself to many and has been an inspiration to those who know him.

The modern treatment of aneurysm began at the latter part of the nineteenth century with experiments attempting to suture arteries. John B. Murphy in 1897 published a classic paper demonstrating by clinical and experimental work that end-to-end anastomosis of arteries was possible. He successfully performed the first end-to-end anastomosis in a human after excising an injured segment of a femoral artery. The anastomosis was accomplished by invaginating and suturing the proximal into the distal segment of the artery. Payr in 1900 attempted anastomosis of vessels by using magnesium rings. The work which Carrel did from 1900 to 1910 and for which he received the Nobel Prize in 1912 was fundamental and in reality lay recorded as a successful method all these years without use, at least for aneurysms of the aorta, until very recently. He was able to transplant in experimental animals almost with unfailing success large sections of arteries and veins and to unite large vessels such as the aorta and the inferior vena cava. All of this lay dormant until almost simultaneously Crafoord and Gross successfully operated upon coarctation of the aorta by excision of the narrowed segment and anastomosis (1945). This together with the brilliant work of Blalock gave tremendous impetus to vascular surgery. Gross then used homologous grafts to bridge large gaps in wide coarcted segments and still several years went by before on March 29, 1951, a Frenchman, Dubost excised the lower end of the aorta containing an aneurysm and replaced this segment with a homologous graft. Since this time numerous operations have been performed successfully to replace, by grafts, segments of large vessels containing aneurysms. Usually homologous grafts, but in addition plastic material such as vinyon N, have been employed. Numerous investigators and surgeons deserve credit for the brilliant and rapid advances which have occurred in the last few years, notably among whom are DeBakey and Cooley, and Bahnson, Brock, Julian, Blakemore, Hufnagel, Schafer, and others. All of the difficulties have not been surmounted, nor have the advances stopped. At the arch and upper thoracic aorta the problem is increasingly complex and difficult. There, interrupting the circulation completely by cross clamping, even for a brief time, creates back-pressure on the heart and with it the danger of immediate death, and, in addition, sufficient temporary ischemia to the spinal cord to result in paraplegia after recovery from anesthesia. The problem of controlling the circulation long enough to replace a segment of the proximal aorta with a graft becomes the problem of continuing adequate circulation during the time the graft is being placed. So far the two methods which appear most practical are: chilling the patient into a stage of hypothermia during which the circulation and the demand for it are retarded so that complete cross clamping of the upper aorta can be successfully used (DeBakey); and a second method which employs exclusion of part of the lumen of the aorta at two levels with clamps of the Potts or Beck type while a graft is applied around the segment to be removed by two end-to-side anastomoses. The circulation thus may continue through part of the aorta even at the level it is partially clamped. Additional methods have been suggested but these two at the present seem more feasible.

Lateral excision of saccular aneurysms is itself a significant advance, but it does not have the same appeal of surgical exactness represented in the more complete eradication and replacement of an entire segment by a graft.

Other problems must be solved, but aneurysms of the aorta can no longer be said to be among the unconquerable lesions totally resistant to the efforts of surgeons. Today, at least in some cases, results which can be classed as cures may be obtained.

THE USE AND ABUSE OF DIAGNOSTIC AIDS

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IT IS APPARENT to all that advances in medical and surgical therapy have been quite as dependent upon improved diagnostic aids as upon the development of specific methods of treatment. With the introduction of each new diagnostic procedure there is an accompanying obligation not only that it be utilized fully in cases in which it can be reasonably expected to contribute information of real value in understanding and managing the particular condition under study, but also that it not be employed when simpler, safer, and less expensive means provide all the information required.

Unfortunately, such diagnostic aids are often abused and are employed not because they are really needed for the best care of the patient, but simply in order to add additional weight to conclusions which otherwise can be based upon a solid foundation. In addition, they seem to be utilized with particular frequency if the information obtained lends itself to graphic portrayal in photographs, drawings, charts, or tables. Such information may be important in the development of a new concept and in the clear dissemination of new contributions, but its acquisition certainly cannot be justified simply in order to provide nice photographs, roentgenograms, or charts.

The unjustified use of diagnostic procedures is bad enough if it does nothing more than add to the already overwhelming burden of professional and hospital costs. When it entails a real hazard to the patient it must be condemned most emphatically. Unfortunately such is the case with a number of the procedures which are not infrequently employed unnecessarily.

Angiographic studies serve as a good illustration of this point. They have led to a better understanding of the various cardiovascular disorders and the resultant physiologic disturbances. They have helped to clarify the type of therapy indicated. Once these pioneer studies have been completed, we are left with certain specific indications for the employment of such studies but certainly with no license for their general and indiscriminate use. Their unnecessary utilization not only is a waste of time, effort, and financial resources, but constitutes an unwarranted hazard to the patient. In spite of all precautions that may be taken, the intravascular injection of radio-opaque material is not without danger. Alarming general reactions may occur and, though fortunately they are rare, fatal reactions may take place. Local reactions also occur from time to time. They vary from relatively inconsequential superficial phlebitis following intravenous injections to rare but tragic loss of limb following arterial injections. The true incidence of these reactions is undoubtedly higher than one would judge from the number of cases reported. Once attention is called to the possibility of such

ccurrences there is little tendency for con-nued reporting of them.

The importance of angiographic studies f the cerebral circulation in establishing ie diagnosis of arterial aneurysms and ther vascular conditions and in localizing iem accurately is well recognized. Their ilization in the localization of certain nvascular cerebral tumors is also well es-blished. No one, however, would feel that ey should be used routinely for all sus-cted or proved cases of intracranial sease.

Angiocardiographic studies have contrib-ed much to a better understanding of the natomic and functional pattern in various pes of cardiac abnormalities. Angiocardi-graphy may prove the single most reliable iagnostic study in certain unusual and un-ommon types of cardiac malformation. The vast majority of such cases, however, equires no such studies. The diagnosis can rdinarily be established with relative cer-tainty by simple methods of physical ex-amination, electrocardiographic study, and fluoroscopic and x-ray examination. In most of those instances in which additional information is necessary, procedures such as cardiac catheterization generally pro-vide more useful information at less risk than angiocardiography.

Venographic studies have added much to our knowledge of the various venous dis-orders and the anatomic and functional ab-normalities which characterize varicose veins and venous thrombosis. They have helped to clarify certain problems of therapy in the postthrombotic state by demonstrating that the recannulized vein, contrary to generally held opinion, does not contribute to venous stasis by permitting regurgitant flow of blood. On the other hand, in spite of its distorted and valveless lumen, it contributes to the proximal propulsion of blood. Veno-graphic studies have emphasized very graph-ically the harmful effects of quiet depend-ency in increasing venous stasis and the benefit incident to active muscular exer-cise. Undoubtedly, from time to time, one may meet with a clinical problem so baffling that venography may be required to clarify it. Such cases must, however, be rare in-deed. Ordinarily simple and reliable meth-ods of physical examination permit one to make a clear diagnosis and to outline the proper course of treatment.

Arteriographic studies may occasionally be needed in order to establish precisely the localization of an aneurysm or an arterio-venous fistula, but almost always the lesion can be diagnosed properly, localized accu-rately, and proper treatment can be outlined without such studies. Let us consider, for example, the case of aneurysms of the ab-dominal aorta. The primary problem re-lating to the feasibility of surgical excision and interpolation of an aortic substitute concerns the upper limit of the lesion. If it originates below the level of the renal arter-ies such surgical treatment is feasible. Near-ly all cases of aneurysm of the abdominal aorta do arise below the level of the renal artery. In the exceptional instance the sur-geon may think it wise to carry out some palliative procedure such as internal wiring. It is, therefore, difficult to justify the use of aortography prior to surgical exploration.

Arteriography is certainly not required in the ordinary diagnosis and management of obliterative arterial lesions. It may be justi-fiable in some cases of suspected segmental occlusion and many surgeons believe that it is a necessary aid in such cases. One can, however, use a different plan of attack. The upper limit of the occlusion is almost always identifiable from simple palpation of the pulses. Here we are concerned with the extent of the thrombosis and whether its lower limit is in one of the main arterial pathways or extends peripherally into the small branches of the leg. In the former res-toration of blood flow through the main arterial pathways is a possibility either by a grafting procedure or by thromboend-arterectomy. In the latter such surgical accomplishments are impossible. In cases of aortic or iliac thrombosis one can first ex-plore the femoral artery. This is a quick,

simple, and safe procedure. If the artery is patent and not too badly diseased one knows without further information that restoration of the arterial pathway is a surgical possibility. Similarly, if the femoral artery is obstructed, one can readily gain the information he desires by simply making an incision over the distal portion of the femoral vessels and determining by exploration whether the distal part of the femoral artery and the popliteal are patent, or whether, on the other hand, the popliteal artery is obstructed throughout its entire course. If one finds it impossible to open the main arterial stem, he may proceed at this time to perform a lumbar sympathectomy. As experience is broadened in the management of problems of this sort the specific indications for arteriographic study will be better clarified. Though, undoubtedly, preliminary arteriography may be wise in exceptional instances it is not necessary in the investigation and treatment of many suspected cases of segmental occlusion.

Surely there can be no justification for the use of arteriography in the localization of peripheral arterial emboli, and it is distressing to find that some recommend that all patients with peripheral arterial embolism be examined by aortography. By simple methods of physical examination—palpation of the pulses, determining the level of coldness, hypesthesia or anesthesia, and paresis—one can establish accurately and quickly the precise level of obstruction and can then proceed without delay to carry out arterial embolectomy. To subject such patients to aortography not only exposes them to the risk of this unnecessary and not absolutely safe procedure, but at the same time delays surgical treatment of a condition in which every effort should be bent toward avoidance of delay.

Angiographic studies, like many other diagnostic procedures, have played a most important role in providing us with more precise anatomic and functional information about a variety of cardiovascular conditions. They have proved invaluable in the recognition and localization of certain of these disorders and should be used when they can be anticipated to yield important information not obtainable by simpler and safer methods. Such studies are also justified in an effort to gain new knowledge through carefully planned investigative programs. Otherwise, angiographic studies must be considered unnecessary and potentially hazardous. The same considerations apply to many other diagnostic aids. Their maximum contribution to the care of patients comes from their proper use and the avoidance of their unnecessary employment.

THE SURGEON AT WORK

RECTOSIGMOIDECTOMY PROCEDURES FOR CARCINOMA OF SIGMOID AND RECTUM

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IN PREVIOUS REPORTS we have described the technique of operations which have been labelled rectosigmoidectomy No. 1 and rectosigmoidectomy No. 2 for carcinoma of the lower sigmoid and rectum. Changes and improvements in technique have been developed which have lessened complications in our cases and one feels warranted in making this report. In this article, the controversy of abdominoperineal resection versus radical rectosigmoidectomy with preservation of the anal sphincter mechanism will not be discussed. However, data on our rectosigmoidectomy procedures are now being collected, and the initial analysis leaves us with the impression that the recurrence and apparent curability rates are practically the same for both procedures. A detailed report will be made at a later date and should bring valuable evidence for or against these two sphincter-preserving operations.

We have always admitted that these rectosigmoidectomy procedures were threatened with more complications than the abdominoperineal resection. The most annoying complication in our experience has been the development of a posterior discharging fecal fistula, as we always drain the presacral area through a coccygeal incision. The appearance of such drainage indicated failure of the suture line because of inadequate vascularization followed by necrosis, or an inadequate suture line because of faulty suture technique. In either event, a change in suture technique and a varying type of decompressive procedure has lessened posterior fistula development.

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In our earlier cases, about 20 per cent of the patients developed some apparent fecal drainage following rectosigmoidectomy No. 1, which is anterior dissection, resection, and anastomosis, with the entire procedure done through the abdominal incision, but the presacral space is drained posteriorly by a small incision alongside the coccyx. About 40 per cent of the patients developed posterior fecal drainage following rectosigmoidectomy No. 2 which is abdominal dissection followed by removal of the coccyx and posterior resection and anastomosis with drainage established at the site of the posterior incision. In our original technique, we established a cecostomy for the decompressive measure in both the No. 1 and No. 2 procedures. When posterior fecal drainage developed, it would continue for several days up to 4 months, but in most patients the posterior drainage ceased in 1 to 3 weeks. In 2 patients following rectosigmoidectomy No. 1 and in 3 patients following rectosigmoidectomy No. 2, it became necessary to establish a temporary colostomy of the transverse colon before satisfactory healing occurred. However, we were eventually able to close the colostomy in these 5 patients. Incidentally, 3 of these patients are now living beyond 3 years, 1 beyond 2 years, and 1 died of recurrent carcinoma.

One of the patients now living beyond 3 years had a rectovaginal fistula as well as a posterior fecal draining sinus, both of which closed satisfactorily following colostomy and did not recur

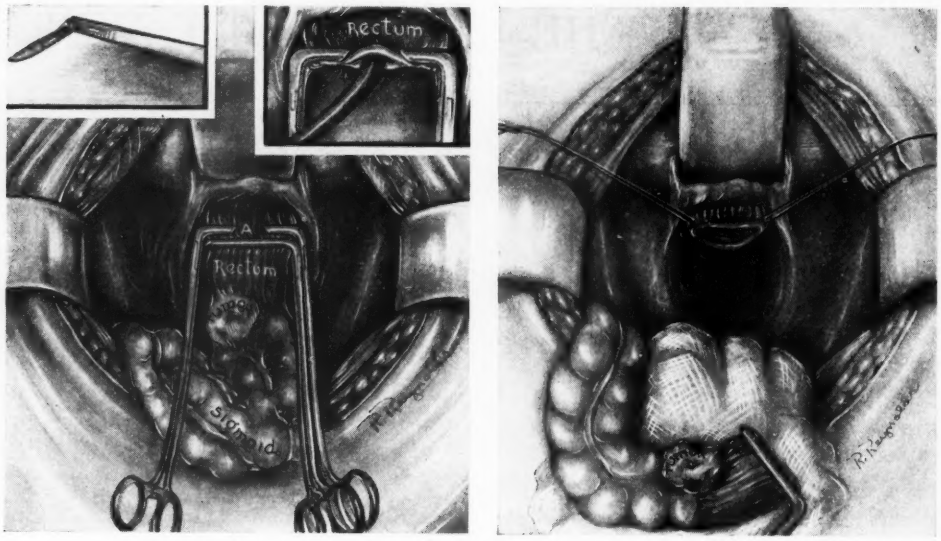

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Fig. 1.

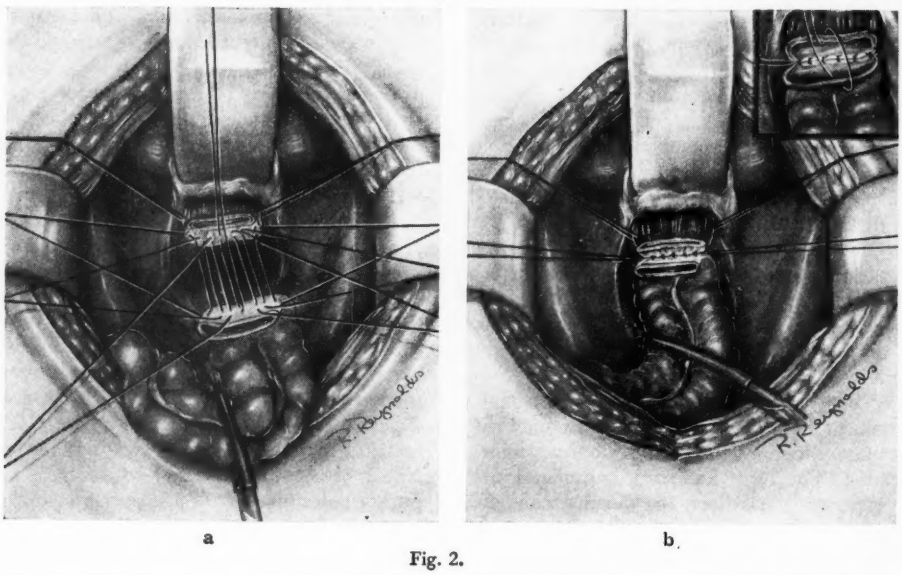

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Fig. 2.

FIG. 1. a, Rectosigmoidectomy No. 1 with rectum dissected free as in abdominoperineal resection. Special clamps applied at least 1½ inches below the lesion. This procedure is done entirely from within the abdomen. b, Following transection of the rectum between the special clamps, the lower rectal segment is steadied by the lower clamps until replaced by a guy suture at each angle.

FIG. 2. a, Long interrupted No. 000 silk sutures piercing the seromuscular and muscular layers are inserted but not tied until all are in place. b, The sutures are tied and all are cut except the angle sutures. Interrupted No. 00 chromic catgut sutures unite the mucosal layers posteriorly. On the anterior wall similar catgut sutures are placed with knots always on the mucosal surface.

when the colostomy was closed. Another patient also developed a rectovaginal fistula and a posterior fistula, both of which closed in 6 weeks without a colostomy.

Our first step to overcome this annoying complication was to analyze critically our suturing technique. In our earlier descriptions of the technique for rectosigmoidectomy No. 1 and No. 2, the catgut sutures with knots on the mucosal side were placed first and then the figure-of-eight silk sutures were placed as a second layer. In the No. 1 operation, we frequently had difficulty in placing the silk sutures on the posterior wall toward the sacral side, and no doubt this proved to be a weak area in the anastomosis. Likewise, in the No. 2 operation, the catgut sutures with knots on the mucosal surface were placed first. In this No. 2 procedure, we frequently had difficulty in placing the interrupted silk sutures on the anterior wall toward the prostate or vagina and no doubt this proved to be a weak area in the anastomosis.

In the rectosigmoidectomy No. 1 procedure, we now insert a posterior row of seromuscular-muscular silk guide sutures, then after all of these are in place the proximal colon is brought down into position against the rectal segment and the sutures are tied (Figs. 1 and 2). This gives good apposition of the serosal wall of the upper segment against the muscular wall of the rectal segment. With completion of tying this posterior layer of silk sutures, interrupted catgut sutures approximate the mucosa on the posterior wall and then are continued anteriorly, always with the knots on the mucosal side for the purpose of inversion. The anterior layer of interrupted figure-of-eight silk sutures is then completed (Figs. 2 and 3). As described previously, a drain is placed in the hollow of the sacrum where the tissues have been separated in the presacral and precoccygeal areas as in the abdominoperineal technique. At the conclusion of the operation, a small incision is made alongside the coccyx and the drain delivered. We have been removing this drain on about the third day. A supplemental cecostomy for decompression is always established following the rectosigmoidectomy No. 1 procedure and a No. 36 mushroom catheter is used. Usually we do not connect it to a suction apparatus and it is irrigated with 30 cubic centimeters of water night and morning. About the sixth or seventh postoperative day, increasing amounts of water, varying from 60 to 120 cubic centimeters, are instilled through the cecostomy tube, and bowel evacuation is encouraged by this method rather than by rectal instillations which would more likely disrupt the site of anastomosis by sudden distention or by direct contact of the enema tube. This cecostomy tube is removed between the tenth and fourteenth day, or as soon as the patient has had several bowel evacuations. The cecostomy incision has always closed without further formal surgery. By making these few changes in the suturing technique, we have practically eliminated fecal drainage through the posterior drainage site following the No. 1 procedure. This No. 1 procedure is indicated for lesions of the lower sigmoid and the rectosigmoid area. If the lesion is entirely below the peritoneal reflection on the floor of the pelvis or if the lesion is less than 10 centimeters (4 inches) from the external anal margin, one should resort to the No. 2 rectosigmoidectomy. At the present time, it is controversial in our own minds as to whether recto-

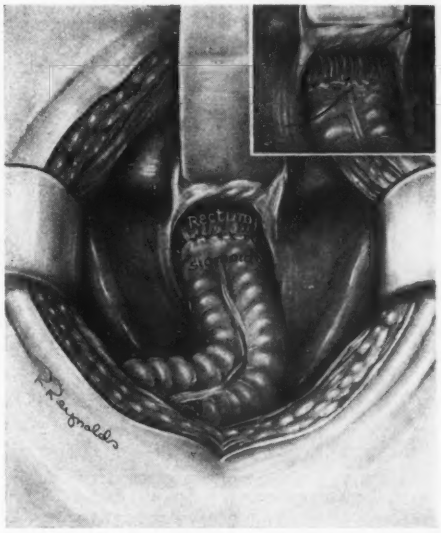

FIG. 3. The anastomosis is completed by inserting a row of interrupted No. 000 figure-of-eight silk sutures on the anterior wall and angles. A drain is placed in the hollow of the sacrum where tissues have been freed into the coccyx area. The drain is brought out posteriorly by a small incision along the coccyx at the conclusion of the operation. The peritoneal floor is reconstructed above the suture line. A tube cecostomy is established through a small stab incision using a No. 32 to No. 36 mushroom catheter and the cecum is fixed to the parietal peritoneum.

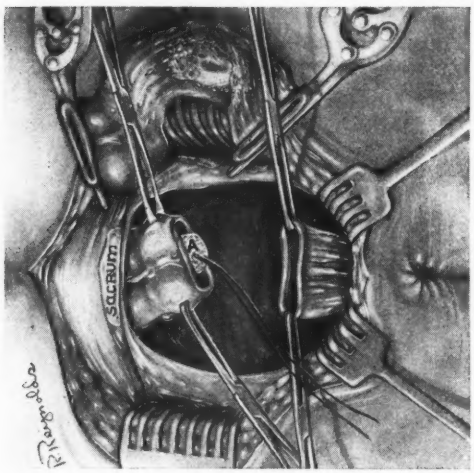

Fig. 4. Rectosigmoidectomy No. 2 is abdominal dissection as with abdominoperineal operations but the resection and anastomosis are accomplished through a posterior incision after removal of the coccyx. A heavy black silk ligature is placed around the bowel to identify the level of adequate blood supply and level for anastomosis. The peritoneal floor is established loosely around the colon to permit it to be drawn into the posterior incision for resection and anastomosis. The levator structures are excised widely. A pledget of gauze secured with a suture is placed in bowel lumen to avoid the necessity of a clamp and is removed just before completion of the anastomosis.

sigmoidectomy No. 1 or rectosigmoidectomy No. 2 should be done for those lesions in which the lower margin of the lesion is between 10 centimeters (4 inches) and 12½ centimeters (5 inches) from the external sphincter margin. This distance from the external sphincter margin is also a variable because at operation one often finds that some intussusception has taken place or that the S-shaped conformity of the upper rectum and rectosigmoid has been deceiving. It seems as though the location of the lesion as related to the peritoneal floor is just as important and that both factors should be taken into consideration in selecting the type of operative procedure. At the present time, we use the following key to determine the type of operation.

1. Level from external sphincter margin:
   a. 5 cm. or less—abdominoperineal resection.
   b. 5 cm. to 10 cm.—No. 2 procedure.
   c. 10 cm. to 12 cm.—No. 1 procedure (?).
   d. 12½ cm. or more—No. 1 procedure.
2. Relation to peritoneal reflection on pelvic floor:
   a. If lesion is entirely below—No. 2 procedure.

As our experience with rectosigmoidectomies increased, we became convinced that lesions with the lower margin between the 5 centimeter (2 inch) and 10 centimeter (4 inch) level from the external anal margin, or those lesions below the peritoneal reflection should be removed by abdominal dissection with posterior resection and anastomosis, which we prefer to call the rectosigmoidectomy No. 2 procedure. This operation permits radical abdominal dissection for the upward spread of the disease, and the posterior approach permits wide lateral dissection of the levator ani area. When the lower margin of the lesion is less than 5 centimeters (2 inches) from the external anal margin, abdominoperineal resection is recommended. About 40 per cent of the patients following rectosigmoidectomy No. 2 developed some fecal drainage, and although many of them cleared up in a few weeks, we were convinced that a critical analysis should be made of our suture technique and that consideration should be given to establishing a colostomy of the transverse colon rather than depending upon a cecostomy. The following procedure was developed. The abdominal dissection is carried out as one proceeds for an abdominoperineal resection. The level for later transection of the left colon or sigmoid is selected where the bowel is viable, and it is determined whether or not sufficient left colon is available for anastomosis to the lower rectum or anus. This level is marked by tying a piece of heavy black ligature around the bowel for later identification through the posterior incision. The peritoneal floor is reconstructed around the bowel but not too tightly as to interfere with delivery of the bowel into the posterior incision. As stated previously, we have changed our minds and have concluded that a colostomy of the transverse colon through a small transverse incision above the umbilicus is indicated in rectosigmoidectomy No. 2, and that one should not depend upon a cecostomy as in rectosigmoidectomy No. 1. The abdomen is then closed, and the patient is turned upon his left side for the posterior resection and anastomosis. A suction catheter is inserted through the anus for a few minutes to remove the rectal contents which have been compressed downward from the colon. An adequate skin incision is made to remove the coccyx, and this usually extends to within 2 to 3 centimeters of the anal margin. The fascia propria is opened to enter the pre-

sacral space, followed by wide transection of the levator ani structures. The sigmoid is then delivered by traction and the level of proposed colon transection is identified by the black silk ligature. The time element has afforded further evaluation of bowel viability at this level. A crushing clamp is applied at the ligature level, Allis forceps are applied just above the clamp and the bowel is transected between the Allis forceps and the crushing clamp. As the colon is opened, suction is momentarily applied, and then a half piece of 4 by 4 gauze secured with ligature material is placed in the bowel lumen. This absorbs and prevents leakage of secretions and the ligature permits easy removal of the gauze later. A crushing clamp is then placed across the lower rectum, at least 1½ inches and preferably 2 inches, below the lower margin of the tumor. By means of an irrigating syringe and suction apparatus, the rectal segment below the crushing clamp is thoroughly irrigated in the hopes of removing any loose, viable cancer cells. Allis forceps are applied just above the anal sphincter level, which usually can be readily identified, and the rectal segment is transected just above these controlling Allis forceps (Fig. 4). One is now ready for the anastomosis, and here again we have improved the technique by first inserting the layer of interrupted No. 000 silk figure-of-eight sutures on the anterior wall toward the prostate or vagina. These sutures are not tied until all the silk sutures have been placed. The anterior layer of interrupted catgut sutures with knots on the mucosal side are then inserted. This layer of sutures is then continued onto the posterior wall, with knots on the lumen side, and before completion of the suture line the gauze pledget is removed. The anastomosis is then completed by continuing the interrupted figure-of-eight silk sutures onto the posterior wall (Fig. 5). A drain is inserted into the presacral space away from the suture line, and is brought out near the upper angle of the incision. The drain is removed in about 3 days. At the present time, we are closing these colostomies in about 8 weeks following resection. In the interval, the anorectal anastomosis should be examined by gentle insertion of the index finger about 10 days following resection, and then every week or so until the colostomy is closed. If the anastomosis admits the index finger, it is adequate. A few patients have needed additional dilatations before closure of the colostomy. The colostomy is usually eradicated by resection and end-to-end anastomosis.

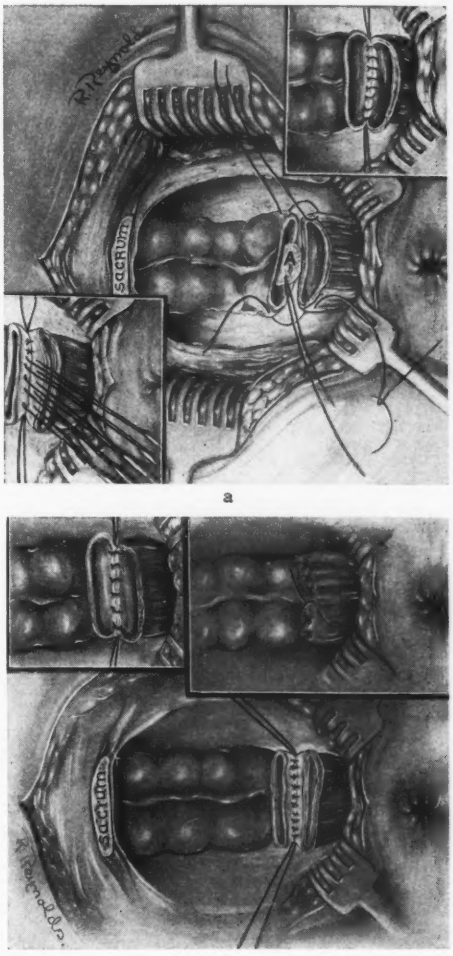

FIG. 5. a, The seromuscular and muscular interrupted sutures of No. 000 silk have been placed at each angle, followed by insertion of a complete layer of such sutures on the anterior wall. After all sutures have been placed they are tied. The mucosal margins on the anterior wall are then approximated with interrupted No. 00 chromic catgut sutures. These sutures are continued onto the posterior wall with knots on the mucosal side. b, After closure of the mucosal layers on the posterior wall, the anastomosis is completed with a layer of interrupted No. 000 figure-of-eight silk sutures. A drain is placed away from the suture line and brought out through the inision.

We have varied the type of abdominal incision for rectosigmoidectomy, using a left para-

median incision, a lower abdominal transverse incision angling upward on the left abdomen to the costal arch, a long crescent type incision across the abdomen just below the level of the umbilicus, and an oblique incision extending from the right lower quadrant across and upward to the costal arch. There are advantages and disadvantages with each incision. It is always advantageous if the assistant standing on the right side of the patient is capable and takes over the freeing and mobilization of the splenic flexure by using long dissecting scissors because he is much better able to do this under direct vision.

In our rectosigmoidectomy cases, we usually ligate the inferior mesenteric vessels just below the left colic branch. On some occasions we have ligated just below the first sigmoid vessels and at other times have ligated the inferior mesenteric at its aortic origin. Our general policy is to remove any large gland encountered along the upper superior vessels, have a frozen section study made, and if reported back as containing cancer cells, a higher ligation is done. Marked invasion of this central group of glands precludes much hope for a cure and probably these cases should be classified as palliative resections.

In a previous report, we have described a rectosigmoidectomy No. 3 which was an operation done entirely through a posterior approach, i.e., posterior dissection, posterior resection, and anastomosis. This operation was reserved for very poor risk patients and was always labelled as a poor cancer operation. At the present time, we have discarded it and only use the rectosigmoidectomy No. 1 and No. 2 procedures.

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The Book Shelf

BILLROTH AND BRAHMS

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THE FRIENDSHIP between Billroth and Brahms began in the year 1866 and ended with Billroth's death in 1894. They first met in the Spring of 1866 in Zurich where Theodor Billroth, at the age of 37, was chief of the Surgical Clinic of the University. He had held this position for 7 years and had attained a reputation throughout Europe as a surgeon of genius. Johannes Brahms, 33 years old, had made a name for himself as a composer, pianist, and conductor.

When Brahms stopped in Zurich on a concert tour, Billroth invited him to a musical evening in his home. In one of his letters Billroth describes the occasion. He and his friends had practiced diligently the difficult Second String Sextette of Brahms. Billroth played the viola. The doctor, who was accustomed to lecture and to operate in front of an audience of students, was not so sure of himself as a viola player before a circle of musical experts. And he was awed by the presence of the admired composer. In the middle of the performance Billroth started to perspire and tremble and finally had to stop playing. Fortunately another viola player was present to take over his part. Billroth closes his letter as follows: "I realized the agony which Brahms must have suffered during our performance, but he took it in a charming manner." In the succeeding weeks Billroth and Brahms saw a great deal of each other and before the summer was over they had become close friends.

In Brahms, Theodor Billroth found the realization of his own early dream of becoming a great musician. Since childhood Billroth had shown a decided musical talent and this had been fostered by his maternal grandmother, once a celebrated singer at the Royal Opera at Berlin. Theodor loved to practice the piano at the expense of his lessons in Latin, Greek, and mathematics. His father, a poor preacher, had died from tuberculosis when Theodor was only 5 years old and the eldest of 4 sons. His mother, suffering from the same disease, was hard pressed to pay for all the tutoring necessary to get Theodor through high school. Finally he squeezed through, 2 years late. He still yearned to become a professional musician, but a family council which included an uncle who was a prominent physician decreed that young Theodor must take up the safer and more respectable career of a doctor of medicine. Bitterly disappointed, Theodor registered at the medical school at Greifswald. He rarely attended any lectures during the first semester, spending his time pounding the piano and studying music.

A sudden change came over Billroth in his second semester when a family friend, Dr. Wilhelm Baum, succeeded in arousing Billroth's interest in medicine. From this time forth he devoted his life to the calling of medicine though he could never forget his first love, music, to which he was faithful all his life. Billroth finished his medical studies in Berlin, graduating in 1852. From 1853 to 1859 he was assistant to Langenbeck, director of the surgical department of the University of Berlin. Billroth's chief interest during this time was pathology, and he made valuable contributions to the science of

pathology as the basis of modern surgery. In 1859 Billroth accepted a call from the Medical School of Zurich to become chief of surgery.

In his first years in Zurich he had little private practice, and his duties as head of the clinic and as teacher left him sufficient time for scientific research and writing. Like other men of genius Billroth was endowed with a remarkable capacity for work combined with an extraordinary versatility, and was driven by a restless energy to give expression to his varied talents. Out of boredom, he says, he compiled the handbook, "General Surgical Pathology and Therapy," which was published in 1863 and became the standard textbook of the time. In Zurich Billroth also composed three trios, a piano quintet, and a string quartet. In one of his letters he writes that he surrendered these compositions to the flames some years later—"It was awful stuff and stank dreadfully as it burned." Frequently Billroth acted as music critic for newspapers and magazines and he even served as guest conductor for the Music Society of Zurich on two occasions.

Most of all he enjoyed playing the piano and participating in the making of music. Among the personnel of the University he found several excellent musicians, and with these he formed a group which played chamber music in his house at least once a week. Billroth's enthusiasm for music for strings of the classical composers, and of the young Brahms, was so great that he studied the viola in order to be able to participate in performances of pieces written for strings only. And all his life Billroth was a prolific writer of letters. The collection of these letters, published after his death, read like a personal diary and show a great facility for literary expression.

Early in 1867 Billroth accepted a call from the University of Vienna to take over the direction of the first surgical clinic. By this time Brahms had established his permanent residence in a flat in Vienna where he lived when he was not traveling on concert tours in the winter or taking vacation trips in the summer. Vienna received the two friends with open arms and encompassed them with warmth and gaiety. It became their home where they spent the greater part of their mature years and where they were finally buried. A strange kinship and understanding existed between Billroth and Brahms which drew them together from the first; a certain parallelism of their ancestry, their backgrounds, and their lives, a similarity of their looks, their characters, their philosophy, and their tastes. On their fathers' side both men were of Scandinavian extraction and of Protestant faith. They were born on the misty seashore of Northern Germany hardly 150 miles apart. Four years separated the dates of their births and only 3 years were to separate the time of their deaths. There was a certain likeness in their physical features. Both men had penetrating blue eyes below high, open foreheads; both had strong noses though Billroth's was more narrow and aristocratic than the broader nose which Brahms inherited from his peasant ancestors. When they first met Billroth was already flourishing a well kept professorial beard. Brahms was still smooth-shaven. Their personal likeness increased when Brahms also grew a beard which surrounded his face with a flaxen frame. The two friends had broad shoulders, large torsos, and were inclined to corpulence. Billroth was a tall man and carried his 230 pounds with dignity, whereas Brahms had short legs and came to look like a barrel. Both men liked to eat and drink heartily and to smoke big black cigars in an endless chain. Brahms was never seriously ill and was unconcerned with his health and weight. He did not change his mode of living until his last sickness wasted his body. Billroth, the only member of a tubercular family of 6 to reach middle age, was plagued all his life by various respiratory allergies. In his thirties he suffered from his first gallstone colics and in later years he was also tormented by kidney stones. Six years prior to his death he had a severe attack of pneumonia from which he never completely recovered. Thereafter he suffered with increasing frequency from episodes of angina and decompensation of the heart. All during his later life Billroth made heoric attempts to reduce with all kinds of rigid diets. He even gave up the favorite little chocolates which he used to carry in his pocket.

Billroth and Brahms grew up in the twilight of the nineteenth century romanticism which suffused the cultural atmosphere of Europe with a hue of sadness and nostalgia which was to be reflected in the music of Brahms. Both men were bearing the scars of a childhood of insecurity and poverty. After the early loss of his father Billroth had had to depend upon relatives for support and education. Brahms, the son of a

poor bass player, had been reared in an evil-smelling tenement house close to the red light district of Hamburg. In his boyhood he had to play the piano in the dives and music halls of the neighborhood in order to contribute to the upkeep of his family and to pay for his musical training.

A critical intellect hindered Billroth and Brahms from embracing without reservations the rugged faith that had been the fortress of their fathers. They had to look to philosophy for guidance, and in the spirit of the time came under the pall of the pessimism of Schopenhauer. Billroth wrote in one of his letters to Brahms, "We are kindred spirits, free of odious optimism, matured in sorrow." Fortunately both men had been endowed with the great gift of humor and the enjoyment of a hearty laughter which balanced the serious side of their characters. Even though the friends could not accept the doctrines of the church, they could never erase from their memory the impressions of their childhood religion. Brahms found inspiration in the Scriptures for his famous Requiem and for the beautiful "Four Serious Songs," his last composition. Billroth, in his last Will made the special request that no autopsy be performed on his body; the religious background of the son of a Lutheran minister and brother of two clergymen prevailed against the reasoning of the pioneer pathologist.

Some fundamental characteristics common to Billroth and Brahms were their humility, honesty, and their capacity for friendship. Billroth was deeply moved when Brahms dedicated two of his string quartets to him, and voiced his belief that his name on the title page of Brahms' Opus 51 would outlive his fame as a surgeon. Rarely did he ever mention his own achievements, and he claimed with pride that the youngest assistant in his clinic could perform the most difficult operations as well as he could. He was the first surgeon to insist upon accurate statistics based on the follow-up of patients. The great Russian surgeon, Pirogoff, who came to him for extirpation of the tongue, wrote him, "You are the first (surgeon) to tell the truth."

Billroth's clinic was the training school of a score of outstanding surgeons of the time; among them Mikulicz, Czerny, and Eiselsberg. His assistants became his lifelong friends and he spared no effort in promoting and placing them in leading positions as directors of surgical departments of medical schools and hospitals all over Europe.

Like Billroth, Brahms never lost his sense of humility. He felt inadequate in the shadow of the great masters—Bach, Mozart, and Beethoven—and strove incessantly to reach their musical heights. Personal praise embarrassed him. Once during a banquet Joachim, the famous violinist, proposed a toast to Brahms. As he was closing with the words, "So let us raise our glasses to the greatest composer," Brahms jumped to his feet, glass in hand, and interrupted, "Yes, let us drink to Mozart." Many of the contemporary composers were friends of Brahms, among them Max Bruch, Johann Strauss, and Antonin Dvorak. It was Brahms to whom Dvorak sent the manuscript of the New World Symphony from New York to proofread and transmit it to his publisher.

The similarity between Billroth and Brahms ended if one looked at their clothes. Billroth was always well dressed and groomed, as became his position; Brahms, generous in other respects, had inherited from his peasant ancestors his dislike of spending money on his habit. Most of the time he wore old, patched-up suits with ragged pants always too short. He had a special aversion to dressing up for an occasion, as if it meant to disguise his real self. The wits of Vienna claimed that Brahms let his beard grow to such length in order to hide his bare neck as it emerged from an open shirt without collar and tie. Brahms' refusal to wear a dress-suit led once to a temporary estrangement between him and Billroth's family. Brahms had been asked to a banquet in Billroth's home and Billroth's wife and daughter were embarrassed when Brahms appeared in his old rags. On a later occasion Billroth sent an invitation to Brahms begging him to be his guest at the opening ceremony of the new quarters for the Society of the Physicians of Vienna, the pride and joy of Billroth who had served as president of the Society for 6 years. As a special inducement, Billroth added that Brahms did not need to wear a formal suit and could slip in through a side entrance to the gallery.

Brahms' refusal to comply with convention in his clothing was only one of the expressions of his social maladjustment which distinguished him from the better adjusted Billroth. Playing the piano in the lower resorts of the harbor area, Brahms early came in close contact with

the scantily dressed street girls who populated the district and who liked to pet the handsome and talented youth. These boyhood experiences influenced Brahms' future attitude toward women. All his life he felt at ease in the company of street girls and uncomfortable in the society of other young women. He was more attracted to older women of refinement; they reminded him of his mother whose memory he immortalized in his earliest masterpiece, the German Requiem. In contrast to Brahms who missed the balancing influence of a satisfying female companionship, the life of Billroth was completed by a happy marriage and a family, though his family life was clouded by the early loss of two of his five children, one of them an only son.

The strongest bond of the friendship between Billroth and Brahms was welded by their common love of music and the similarity of their musical tastes. It was no accident that Vienna had become the heart of European music in the eighteenth century, the mother of the music of Haydn, Mozart, Beethoven, and Schubert. In the capital of the Hapsburgs, the confluence of a dozen nationalities, the music of Western Europe mixed with the sounds from the East floating up the valley of the Danube, and with the colors of the South carried across the passes of the Alps. Brahms, the successor of the great masters, experienced an exhilaration similar to theirs from the musical climate of Vienna. Here he was close to the sources of the strange and exciting melodies which emanated from the plains of Hungary. In the 1870's the air of Vienna was vibrating with the tunes of gypsy violins and Hungarian dance music seeping from the coffeehouses and music halls. Brahms absorbed these sounds and gave them fresh expression in many of his compositions. His collection of Hungarian dances became his most popular work.

After his arrival in Vienna in 1867 Billroth threw himself with his whole enthusiasm into the musical whirl of the metropolis. During the first 2 months of the winter season he attended not less than 19 concerts. In the same year Billroth made the acquaintance of Edward Hanslik, famous music critic and professor of music at the University of Vienna. Hanslik shared with Billroth a profound admiration for Brahms, and he soon became the third member of their musical brotherhood. In the course of time Billroth, Brahms, and Hanslik formed an artistic triumvirate which for 2 decades exerted a deep influence on the musical life of Vienna.

In those days the musical public of middle Europe and of Vienna took their music seriously. The music lovers were divided into 2 hostile camps. One was following the classical school as expressed in the traditional forms of Bach, Mozart, and Beethoven. In Brahms they thought they had found a reincarnation of the old masters, and his devotees were called, appropriately, "Brahmins" by the Viennese. In the other camp were the followers of a new school of music. Their protagonists were striving for new forms of musical expression in opera and symphony. They were experimenting with new harmonic patterns, and dazzling orchestral effects. Richard Wagner was their idol—he was the prophet of "the music of the future." The unquestioned leader of the Brahmins in Vienna was Billroth, ably assisted by his friend, Hanslik. Strangely enough, the head of the Wagnerians in Vienna was also a prominent physician, Dr. Standhartner, personal physician to the Empress of Austria and generous supporter of Richard Wagner.

No love was lost between the Brahmins, the believers in the true classical music, and the Wagnerian heretics. In newspapers, pamphlets, and open letters they bitterly attacked each other and their idols with barbs of invective and ridicule. The most vociferous and vitriolic spokesman of the Wagnerians was Richard Wagner himself. He called Brahms everything from a plagiarist to a eunuch, whose music was always boring and "as dry as hay in which rarely a kernel of oats could be found," and whose orchestral sounds suggested "the clatter of pots and pans." Wagner was infuriated by the stony silence of Brahms who ignored these attacks and never once replied to them. Finally Wagner hurled his bombshell at Brahms. He proclaimed "the news" that Brahms was not even of Teutonic origin, and that his real name was Abrahams. Brahms merely chuckled and was amused when his friends addressed him as Mr. Abrahams.

Much as Brahms disliked the egotism and megalomania of Richard Wagner, he was compelled to admire his musical originality, and never allowed himself to become involved in the war of words between the Wagnerians and the Brahmins. Quietly he worked on his music and left the talking and arguing to his friends,

especially to the eloquent Hanslik who could hold his own in any contest of invective and sarcasm. Hanslik replied to Wagner in kind, calling him an "anti-melodic fanatic," his music "amateurish, tedious, noisy, and abstruse." The first act of "Die Meistersinger" he described as "dull, dismal, musical mist"; and "Das Rheingold" made him "seasick" as he was being "tossed between laughter and vexation."

Billroth as the high priest of the Brahmins showed his disdain for Wagner in other ways. In some of the concerts that he and his friends attended, inevitably pieces of Wagnerian music would be on the program. On such occasions the Brahmins demonstrated their protest against this musical heresy by leaving the concert hall in a body before the first beat of the conductor could release the flood of brassy sounds. Billroth gave the signal. He would rise from his seat to his full height and march out of the hall flanked by the tall Hanslik. The retinue of faithful Brahmins would close ranks behind them and follow to the nearest exit. The procession ended in the soundproof shelter of a nearby restaurant. There the faithful waited until the last echo of the sacrilegious music would have died away and the usher gave the all-clear signal, when they would return.

During his first years in Vienna, Billroth had not much private practice and had time enough to meet Brahms frequently for lunch at the Blue Hedgehog, a traditional resort of the musicians of Vienna since the days of Schubert. In later years the two friends kept up their close relationship through letters and messages. Brahms liked and valued the musical criticism of Billroth. He often sent him the sketches of his new compositions which Billroth would return with his critical suggestions. After Billroth was well established in Vienna, he bought and renovated an old mansion at the edge of the Vienna woods. All the rooms in his new home he had furnished in simple taste except for a large music room which he had decorated in the regal splendor of the late Renaissance. In this room private concerts were given for many years in which Brahms personally supervised and conducted performances of his newest works before a selected group of guests. After a good performance champagne was served—for less satisfactory performances beer had to do.

Billroth never ceased to be thankful to Brahms for the inspiration and joy which his friendship and his music gave him. In 1887 he wrote to him, "I am grateful for all the beauty with which you have gladdened and enriched my life." In 1890 he wrote, "I was often reflecting upon what constitutes human happiness. Today I was happy hearing your music. When I think back on the hours of my life, always I was the happiest when I could listen to your music." Billroth wrote his last letter to Brahms in January 1894, 3 weeks before his death. It bears the postmark of Abbazia, a winter resort on the Adriatic Sea where Billroth used to take refuge from the rigors of the winters of Vienna. He was sitting in his room propped up in a chair, fighting for breath, but his mind was active. The letter to Brahms discusses the idiom and rhythm of German folk songs and dances and asks his friend for his comments. Billroth was then compiling material for a book about the psychology of musical perception and appreciation, entitled "Who Is Musical?" He was unable to finish the book. After his death it was completed and published by Edward Hanslik.

Three years later Brahms followed his friend. He died from a cancerous obstruction of the biliary tract, resulting in painless jaundice and terminal hematemesis. Up to that time no surgeon had ever successfully operated on such a condition except Billroth who, in 1884, had performed the first pancreatectomy with recovery. Six weeks before his death Brahms had dinner with Billroth's widow in the familiar surroundings of her home. This was one of the last occasions on which he left his flat. Billroth and Brahms were buried in the Central Cemetery of Vienna not far from each other and close to the graves of Beethoven and Schubert.

Reviews of New Books

SEVERAL FACTORS which are of importance in a consideration of artificial hibernation should be mentioned at the outset. First of all there is Claude Bernard's theory of the importance of the "Milieu intérieur" for maintenance of all conditions necessary to life; secondly there is the great development in our knowledge of the autonomic nervous system and the drugs influencing it; and thirdly the role of the endocrine glands in the reactions of the organism to stress —Selye's stress syndrome. Finally there are the new observations of Laborit who in collaboration with many others in recent years has studied hemorrhagic shock and its treatment. All these points have been stressed previously in Laborit's book *Reaction organique a l'aggression et choc.* The authors refer to this book in their introduction and emphasize that anyone attempting artificial hibernation should have a thorough knowledge of it.

Pratique de l'hibernothérapie[1] is actually a clinical manual, written in collaboration with many others, who used the method in several fields of medicine and surgery. It is a symposium with each chapter concerned with observations in a different specialty. Many of the articles are papers which have been published previously in periodicals.

In the first two chapters the physiopathology of therapeutic hibernation is discussed. The third chapter, written by P. Huguenard, is a very comprehensive one, summarizing statistical data, results, indications, contraindications, and complications in general surgery. Preoperative and postoperative management, supportive therapy, and, last but not least, different types of the "lytic cocktails" are discussed in detail. Succeeding chapters relate observations and experiences with the method in treatment of shock, in thoracic surgery, neurosurgery, pediatrics (neurotoxicoses of infants), obstetrics, psychiatry, and medicine. Results observed in medicine are the least convincing. Each article brings specific data, which sometimes are surprising. It is emphasized that hibernation should be "light" in thoracic surgery, since a prolonged state of lethargy in the postoperative period may prevent adequate coughing, so important in these cases. It is pointed out, that replacement transfusions are better tolerated by newborn infants if performed under therapeutic hibernation, since shock, a frequent complication of this procedure, is prevented. Artificial hibernation in cardiac surgery is reported in surgery on dogs only. In the last chapter the possibilities of the use of somatotrophic hormone of the pituitary is stressed.

It is apparent that artificial hibernation is a method, which has been tried in every specialty in medicine and surgery, particularly in difficult and desperate cases. It seems to have been beneficial frequently and when other therapy in similar situations has failed.

Pratique de l'hibernothérapie is an excellent guide for those who want to use the method, since it considers all the possibilities and problems of artificial hibernation. It should, however, include more case reports. A few anesthesia records would also be of great value to the reader. Nothing can give a better idea than actual case reports as to the immediate reactions of an individual patient to different drugs and different conditions. They would also show clearly how unexpected reactions and complications have been treated by experts. —*Eva Kavan.*

THE NEW TEXT entitled *Perimetry*[2] covers the entire subject but the author has adopted what may be considered to be an unconventional approach to the subject.

The book is divided into three parts. Part I presents the fundamentals of perimetry which includes the vocabulary or the language of perimetry, complex terms or phrases, and the fundamental concepts associated with the physiology of vision. This presentation of all the basic terms and phrases at the beginning of the book will be greatly appreciated by students who have found how difficult it is to understand the subject as it is presented in other texts. Part 2 contains the body of the text and under perimetric studies there is a detailed description of equipment, the anatomy and physiology of the entire visual pathway together with the procedures followed in examination, and interpretation of all lesions in each part of the pathway. Functional disturbances are discussed too and there is a good review of the various lesions and their corresponding field defects. Part 3 is devoted to a descriptive and tabular review of perimetry and a discussion of the pitfalls encountered in perimetry.

This new book is a valuable contribution to perimetry. The material is presented in a more complete form and in a more interesting manner than in other texts. The book is well written and it is recommended to all those interested in the subject.

—*Irving Puntenney.*

THE FIFTH EDITION of Partipilo's *Surgical Technique and Principles of Operative Surgery*[3] is a valuable book for all who are interested in surgery. It could well be used as a textbook by interns and surgical residents and would make an excellent reference work for the practicing physician. Basically it is a manual of the operations done by the general surgeon with profuse illustrations of the actual techniques involved and descriptive text material for each. This basic skeleton is richly filled out with well chosen background material summarizing the anatomy, physiology, and often the embryolo-

[1]PRATIQUE DE L'HIBERNOTHÉRAPIE; EN CHIRURGIE ET EN MÉDECINE. By H. Laborit and P. Huguenard. 256 pages, 13 illustrations. 1.400 fr. Paris: Masson & Cie, 1954.

[2]PERIMETRY. By Joshua Zuckerman, B.Sc., M.D., C.M., F.A., C.S. 391 pages, 156 illustrations. $10.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1954.

[3]SURGICAL TECHNIQUE AND PRINCIPLES OF OPERATIVE SURGERY. By A. V. Partipilo, M.D., F.A.C.S. 704 pages, 548 illustrations. $15.00. Philadelphia: Lea & Febiger, 1953.

gy of the particular body system or area to which the individual operations relate. In many instances clinical aspects of the disease for which surgery is planned are summarized and preoperative and postoperative treatment are outlined. This edition has been enhanced by contributions from 10 consultants in different fields of surgery or allied specialties.

The specific makeup of the book consists of 3 general chapters on principles of operative surgery, suture and ligature material, and knots and methods of tying; chapters on thyroid surgery, the surgery of peripheral vascular disease, chest surgery, breast surgery (with a section on radiotherapy of malignant breast lesions), surgery of the kidney, and the principles of plastic surgery; and the more than 30 chapters devoted to operations on the abdominal wall and intra-abdominal viscera. Two additional chapters, on blood transfusion and on fluid therapy, complete the textual material. This simple listing of the subjects does not do justice to the excellent and extensive coverage of the abdomen, several chapters on hernia alone; 3 on gallbladder and extrahepatic biliary ducts; 1 very good one on pancreas; 6 on large bowel, rectum, and anus; 1 on vagotomy alone; many on stomach and small bowel.

An outstanding feature of the book is the profusion of fine line drawings, almost a thousand in number, used to depict operative procedures, anatomic findings, and physiologic changes. These are clear, accurate, and instructive. The opening chapter, on general principles of operative surgery, is particularly good. Every surgeon should read the first section of this chapter, "The Ideal Surgeon." A feature which should be helpful to students is the questionnaire which the author has appended to most of his chapters as a means of reviewing the subject matter of that chapter. It is commendable that all the standard operative procedures are well described and illustrated, and yet the newer ones are not slighted, each being adequately discussed.

Although the author's surgical philosophy is very sound, some surgeons might dispute the implications of his chapter on aseptic anastomosis. The very good chapter on fluid therapy might have been better placed in juxtaposition to the chapter on blood transfusion instead of at the opposite end of the book. A final criticism, again a minor one, is that occasional typographical errors in the section and chapter headings detract from the otherwise excellent format of the book. These shortcomings in no way diminish the value of this work. It would be a good addition to any surgeon's library. —*Benjamin F. Lounsbury.*

A VALUABLE CONTRIBUTION to the literature on the knee joint has been made by DePalma with his new book *Diseases of the Knee.*[1] This monograph begins with a discussion of the evolution of the knee joint through the lower animals up to man. There is a section on comparative anatomy of the knee joint and an account of the assumption of the upright posture, and the role that the knee joint plays in the posture.

[1]DISEASES OF THE KNEE; MANAGEMENT IN MEDICINE AND SURGERY. By Anthony F. DePalma, M.D. 840 pages, 455 illustrations. $20.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1954.

The author progresses through the anatomy and mechanics of the knee joint, and then takes up the various afflictions which may occur in and about this joint. There is a particularly good chapter on afflictions of the menisci and on traumatic lesions of the ligaments of the knee joint. Other chapters include a discussion of congenital and acquired deformities of the knee joint, fractures and wounds about the knee joint, loose bodies, afflictions of the synovialis and bursae of the knee joint, and the various types of arthritis. There is also a chapter on surgical approaches to the knee joint which includes a description of many surgical procedures. The last chapter deals with bone neoplasms in the region of the knee joint.

Throughout the book etiology, pathology, and medical as well as surgical treatment are discussed. Case histories are presented when appropriate, and operative procedures are described in detail in connection with most of the conditions discussed.

This book brings together much of the literature which has dealt with the knee joint in the past and present and is a helpful reference book which will be of value to the general practitioner as well as to the specialist dealing with disorders of the musculoskeletal system. —*William A. Larmon.*

IN HIS INTRODUCTION to *Die Halswirbelsaeule, Pathologie und Klinik,*[2] Dr. Exner states that Schmörl with his monumental work laid the foundation for all further studies on the pathology of the spine. Schmörl dissected and studied 4,000 human spines, but mostly in the dorsal and lumbar region. Therefore, most of the clinical literature on the cervical spine is based on the analogy with the findings in dorsal and lumbar areas. For this reason the author thought it important to make an exhaustive study of the cervical spine in particular.

In the first section of this monograph the embryology, anatomy, physiology, and the technique of x-ray examination of the cervical spine are discussed in detail.

In the second section different pathologic aspects related to the cervical spine are discussed. The discussion of the degenerative changes in the cervical spine is based on the author's own autopsy material. These changes are described in full detail. The author has examined the shoulder joints of the same cadavers in order to find a possible relationship to degenerative changes in the shoulder. A primary relationship, however, is not probable. According to the author not all symptoms of the "cranio-encephale" and "cervicobrachial" syndromes can be explained by compression of nerve roots. The author describes some changes he found in the spinal ganglia caused by pressure of the vertebral artery. Very good photomicrographs are included to show this possibility.

Several clinical syndromes with possible relationship to the cervical spine are described and discussed. For "migraine cervicale" and facial nerve paresis the cause may be in the cervical spine. Shoulder girdle pain is sometimes due to disc prolapse. Periarthritis scapulohumeralis is probably an independent clinical

[2]DIE HALSWIRBELSAEULE; PATHOLOGIE UND KLINIK. By Dr. Med. Gerhard Exner. 140 pages, 42 illustrations. DM 21.60. Stuttgart: Georg Thieme Verlag, 1954.

entity. The scalenus syndrome and the syndrome of cervical ribs are probably also an expression of cervical pathology; akroparesthesia and brachialgia paresthetica nocturna are angiospastic phenomena. Neurovegetative disturbances in the cervical spine might possibly cause disorders such as Sudeck's atrophy and Dupuytren's contracture.

A separate chapter discusses the general treatment; this includes traction, local infiltration with novocain, and stellate block. Surgery is reserved for a very few cases.

This book is well illustrated and a few interesting case histories are included. It is an excellent monograph on the cervical spine, and contains new ideas about the cervical spine as a possible cause of clinical entities involving the shoulder and hand.

—*J. C. Mulier.*

THE SECOND EDITION of the very beautifully illustrated *Atlas of Congenital Anomalies of the Heart and Great Vessels*[1] authored by Doctors Edwards, Dry, Parker, Burchell, Wood, and Bulbulian and published by Charles C Thomas of Springfield, Illinois gives the reader a clear, concise opportunity to study the experiences these authors have had at the Mayo Clinic.

Brief histories of the common and rare congenital anomalies plus the physical findings, electrocardiograms, roentgenograms, cardiovascular physiologic studies, gross pathology, and drawings illustrating the hemodynamics are well presented.

The Atlas is very stimulating and the reader will profit by his study of it. The biographic sketches and photographs of noted contributors to the advances in cardiovascular knowledge adds interest and historic value to the volume.

The authors are to be commended on the new edition with its increased documented findings covering this expanding field of congenital cardiac disease.

—*Egbert H. Fell.*

FRENCH'S *Index of Differential Diagnosis*[2] needs no introduction to the medical profession. The seventh edition edited by Arthur H. Douthwaite continues the tradition of affording a practical index for differential diagnosis of symptoms covering the entire field of medicine, surgery, gynecology, ophthalmology, dermatology, and neurology.

Like previous editions the body of the book deals with symptoms, and the general index of 145 pages at the end of the book is arranged under headings of the various diseases in which these symptoms may occur.

Much new material has been included in the text and that which is obsolete has been deleted in order to bring this reference up to date.

It is highly recommended by the reviewer as a compact but thorough reference book of value to every medical man regardless of his special field of endeavor.

—*Edward W. Gibbs.*

INCLUDED in the *Transactions of the American Goiter Association for 1953*[3] are papers on research and experimental problems; those covering the field of radioactive iodine, in research, diagnosis, and treatment; those devoted to clinical and surgical problems; and a very extensive group dealing with thyroid malignancies. These were read at the annual meeting of the Association in Chicago in 1953.

A comparison of the effects of tri-iodothyronine, a substance isolated from the blood and thyroid tissue, and thyroxin administered to myxedematous patients is made. These tests showed a greater and more rapid effect from the former than from the latter although the duration of its effect was not as long as that of thyroxin.

A study of the thyroid-stimulating hormone of the anterior pituitary in relation to exophthalmos is made showing that the thyroid-stimulating hormone was distinct from that producing exophthalmos. An exophthalmos-producing substance was isolated from the anterior pituitary, the experiments being carried out on a group of Fundulus, a fish used in these experiments. An antigoitrogenic and calorigenic assay of thyroglobulin, desiccated thyroid, and thyroxin by different modes of administration to rats was carried out.

A report of 28 cases of malignant exophthalmos treated by x-rays is given. Therapy was applied to the region of the orbits and pituitary gland. The conclusion is that the treatment is effective in cases of less than 1 year's duration, rarely effective if over 2 years. Orbital decompression for malignant exophthalmos by a simpler technique than that of Naffziger is discussed. The etiology, pathology, and medical treatment are also considered.

The use of roentgen, thyroid, and cortisone therapy for struma lymphomatosa in 62 patients was studied. All these were proved by needle biopsy and the results tabulated.

A study of 6 patients with acute nonsuppurative thyroiditis, treated with ACTH and cortisone, is reported.

A series of papers dealing with radioiodine in the diagnosis and treatment of thyroid disease are presented. An instructive panel discussion of all the clinical and laboratory methods used in the diagnosis of hyperthyroidism is presented. A report of 10 years of experience in the treatment of diffuse hyperplastic goiter is given. It concludes that the treatment is effective in this type of goiter; that the biologic response is gradual; that myxedema may result; that fibrosis and bizarre cellular damage may follow but there is no evidence of malignancy. The histologic lesions of 23 patients treated with radioiodine showed lymphoid degeneration, glandular atrophy, fibrosis, hyaline, and calcific degeneration with giant cell formation, infarction, and hemorrhage and sometimes nodular, probably compensatory hyperplasia.

[1] AN ATLAS OF CONGENITAL ANOMALIES OF THE HEART AND GREAT VESSELS. By Jesse E. Edwards, Thomas J. Dry, Robert L. Parker, Howard B. Burchell, Earl H. Wood, and Arthur H. Bulbulian. Mayo Clinic and Mayo Foundation. 202 pages, 256 illustrations. 2nd ed. $13.50. Springfield, Ill.: Charles C Thomas, 1954.

[2] FRENCH'S INDEX OF DIFFERENTIAL DIAGNOSIS. Edited by Arthur H. Douthwaite, M.D., F.R.C.P. 7th ed. 1046 pages, 731 illustrations of which 200 are in color. Baltimore, Maryland: The Williams & Wilkins Co., 1954.

[3] TRANSACTIONS OF THE AMERICAN GOITER ASSOCIATION, 1953. Annual Session, May 7, 8, and 9, Drake Hotel, Chicago, Illinois. 423 pages, illustrated. $13.50. Springfield, Ill.: Charles C Thomas, 1954.

Studies of the radioiodine uptake of hyperthyroid patients previously untreated and of those having had other treatment show a significant correlation with the serum protein-bound iodine in those having had no previous treatment. In those treated the uptake values show a much greater variation.

A tracer study of 9 cases of thyroid autographs shows growth and functional activity.

Controversial thyroid problems were discussed in the presidential address. The treatment of hyperthyroidism, the incidence and management of cancer in nodular goiter, and some technical phases of thyroid surgery were included.

A very interesting survey was given of goitrous regions over the entire world. In some countries the incidence was more than 50 per cent.

A report on a new antithyroid drug, neomercazol, was presented. This drug is similar to tapazole. The H atom in the tapazole formula is replaced by the carbethoxy group. Doses of 30 to 50 milligrams were given. Rapid improvement followed but patients are not free from disagreeable side effects.

Potassium perchlorate was another antithyroid drug reported. It was used in 24 cases of exophthalmic goiter with doses of 200 milligrams every 8 hours. Gastric symptoms followed in 2 patients. It is particularly useful in patients who do not tolerate the thiouracil group.

Treatment of simple goiter including a complete history of former methods was discussed. Fifty patients with simple nontoxic goiter were reported treated with desiccated thyroid substance. Two to 3 grains daily was the usual dose. A few were given ½ to 6 grains daily. The period of treatment was 5 years. Eighty-seven per cent of the diffuse goiters responded to treatment. Sixty-seven per cent of the nodular variety had a favorable response.

A very instructive panel discussion of adenomatous goiter was held which covered the subject of carcinoma developing in this type of goiter. The medical, roentgen ray, radioisotope, and surgical treatment were included.

A report on the dissection of the recurrent laryngeal nerves in 100 cadavers was given. A marked variation especially of the terminal branches of this nerve was found. As high as 6 terminal filaments were encountered. In the 200 recurrent laryngeal nerves studied, 114 or 57 per cent had a single trunk and 86 or 43 per cent had a divided trunk. Recurrent nerves with divided trunks were found bilaterally in 24 per cent. Injury to only one branch of the nerve with a divided trunk will produce paralysis only in the area supplied by that branch which may be a single muscle or a portion of a muscle. Routine exposure of the recurrent nerve was discussed and recommended in another paper.

A review of the King operation for abductor paralysis of the vocal cords was given with the conclusion that it is anatomically and physiologically the best reconstructive measure available. This was followed by an article on symptom diagnosis and treatment of bilateral vocal cord paralysis.

A series of 8 very valuable papers on thyroid carcinoma was presented. These discussed the incidence of carcinoma in nodular goiter, the uptake of radioiodine by carcinoma of the thyroid, malignant tumors of the thyroid in general, the present day problem of cancer of the thyroid, the treatment of cancer metastasis with thyrotropin and radioactive iodine during thyroid hormone medication, surgical treatment of thyroid cancer metastasis to cervical lymph nodes, and the thoracocervical approach for thyroid cancer. Practically every phase of thyroid carcinoma was well covered by these papers. There is apparently some difference in the incidence of carcinoma in nodular goiters in various localities. While the East Coast statistics show about 10 per cent malignancies, in the Chicago area they are as high as 24.5 per cent. These statistics may be misleading in view of the fact that autopsies on patients with nodular goiter dying of other conditions show a much lower percentage of malignancies than those whose thyroids are removed by surgery.

Thyroid carcinomas are capable of concentrating radioactive iodine depending on the structure of the tumor. Those that are less anaplastic and have a follicular arrangement containing some colloid concentrate it better and those without follicular pattern do not possess this function to such an extent. There is still some difference of opinion as to the extent of the surgery performed for thyroid carcinoma. A paper on the treatment of thyroid cancer metastasis advocates a total thyroidectomy and removal of all accessible metastases. A euthyroid state is then produced with thyroid extract or thyroxin. Tracer studies to locate other metastases are then made. Then thyrotropin is given in doses of 15 milligrams by intravenous or intramuscular injection twice daily. Repetition of the radioactive iodine tracer study is then made, and if there is a significant increase in the uptake by the metastasis or decreased radioactive iodine excretion, then a therapeutic dose is given.

The Proceedings conclude with two research papers dealing with methods of measurement of the iodine concentration and protein binding capacities of the human thyroid gland. From these two measurements the rate of transfer of plasma iodine to hormone iodine can be calculated. The second is on the identification of thyroglobulin in known blood serum after large doses of radioactive iodine.

Most of the papers were liberally discussed so that the reader is given the advantage of various opinions on each subject. Almost every paper is followed by a good bibliography. —*V. E. Chesky.*

THE AUTHOR of *Fundamentals of Neuropathology*[1] has presented his subject in a clearly exposed text of 697 beautifully printed pages and included 786 mostly well chosen illustrations. His main concern in preparing this book was to show that neuropathology in its most lucid and practical form is general pathology with adequately extended consideration of the nervous system. He addresses himself primarily to the general pathologist.

The first chapter deals with autopsy technique, tissue technique, and staining procedures. The normal and pathologic elements of the nervous system

[1]FUNDAMENTALS OF NEUROPATHOLOGY. By William Brooks Dublin, M.D. 685 pages, 329 illustrations. $18.50. Springfield, Ill.: Charles C Thomas, 1954.

are discussed in the second chapter. Congenital anomalies are presented very briefly in the third chapter. Another short chapter deals with the effect of injuries from application of force or from physical factors other than violence or from intoxications upon the nervous system. The three most detailed and important chapters are those dealing with inflammations, tumors, and metabolic disturbances. Another brief chapter is dedicated to disorders of obscure nature, such as neuromuscular disorders, so-called extrapyramidal tract diseases. Wherever possible, correlation is made between lesions and symptoms and the more essential general clinical and pathologic data are presented in relation with the pathologic nature and etiology of the lesions. The author chose his references primarily for practicality and recentness. The publications mentioned in the bibliography are all derived from accessible journals published in English and, therefore, no mention is made of the fundamental work done in the field of neuropathology by the German, the Austrian, the French, the Italian, and the Spanish pathologists and neurologists.

The whole field of pathology of the central and peripheral nervous system is presented in such an authoritative and simplified form that one has the feeling that most, if not all, of the controversial problems in this field have been solved. The directness and simplicity of the subject presentation are attractive and permit easy reading. However, the lack of discussion and the uncritical attitude of the text raise many questions in the mind of the more mature student. —*George Perret.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Urology. Edited by Meredith Campbell, M.S., M.D., F.A.C.S. With the Collaboration of 51 Contributing Authorities. Vols. 1, 2, and 3. 2356 pages, 1148 illustrations. $60.00 per set. Philadelphia and London: W. B. Saunders Co., 1954.

Color Atlas of Pathology; Endocrine System, Including Pituitary, Thyroid, Parathyroid, Adrenals and Pancreas; Gynecology and Obstetrics, Including Reproductive Organs, Breasts; Male Genital Tract; Skin. Prepared under the auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. 450 pages, illustrated with 1032 figures in color on 343 plates. Philadelphia, London, Montreal: J. B. Lippincott Co., 1954.

Fluid Therapy. By James D. Hardy, M.S. (Chem.), M.D., F.A.C.S. 255 pages, 77 illustrations. $5.50. Philadelphia: Lea & Febiger, 1954.

Progress in Clinical Surgery. By Various Authors. Edited by Rodney Smith, M.S., F.R.C.S. 414 pages, 29 illustrations. $7.50. Boston, Toronto: Little, Brown & Co., 1954.

Current Concepts in Digitalis Therapy. By Bernard Lown, M.D., and Samuel A. Levine, M.D. 164 pages, 21 illustrations. $3.50. Boston, Toronto: Little, Brown & Co., 1954.

Hugh Roy Cullen; a Story of American Opportunity. By Ed Kilman and Theon Wright. Illustrated by Nick Eggenhoffer. 376 pages, illustrated. $4.00. New York: Prentice-Hall, Inc., 1954.

La valvola mitrale; aspetti anatomici, fisiologici, clinici e chirurgici. By Michele A. Chiechi and Charles P. Bailey. 561 pages, 158 illustrations. Roma: Società Editrice Il Pensiero Scientifico, 1954.

Plomage in Pulmonary Tuberculosis; Classic Collapse Procedure in Modern Light with a Collective Review of 1004 Polystan Operations. By Jens L. Hansen, M.D. 19 pages, 8 illustrations. $1.50. Copenhagen: Ejnar Munksgaard Ltd., 1954.

Roentgendiagnostik des Schaedels. By Prof. Dr. Willy Loepp and Prof. Dr. Reinhold Lorenz. 579 pages, 613 illustrations. DM 97. Stuttgart: Georg Thieme Verlag, 1954.

Klinische Fehldiagnosen. By Prof. Dr. M. Bürger. 2nd rev. ed. 550 pages, 214 illustrations. DM 59.40. $14.15. Stuttgart: Georg Thieme Verlag, 1954.

Relation of Fibroadenomatosis (Chronic Mastitis) to Cancer of the Breast. By William Kiaer. 159 pages, 71 illustrations. Da.kr. 30. Copenhagen: Ejnar Munksgaard Ltd., 1954.

Stellate Ganglion Block; Techniques—Indications—Uses. By Daniel C. Moore, M.D. 280 pages, 101 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1954.

Nerve Blocks; a Manual of Regional Anesthesia for Practitioners of Medicine. By John Adriana, M.D. 265 pages, 168 illustrations. $6.50. Springfield, Ill.: Charles C Thomas, 1954.

The Management of Endocrine Disorders of Menstruation and Fertility. By Georgeanna Seegar Jones, M.D. 198 pages, 37 illustrations. $5.75. Springfield, Ill.: Charles C Thomas, 1954.

Fluid and Electrolytes in Practice. By Harry Statland, M.D. 206 pages, 30 illustrations. $5.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1954.

Comment traiter la sciatique. By J. A. Lièvre. 124 pages. 550 fr. Paris: Éditions Médicales Flammarion, 1954.

Maladies des os et des articulations. By Stanislas de Sèze and Antoine Ryckewaert. 1218 pages, 391 illustrations. Paris: Éditions Médicales Flammarion, 1954.

The Foundations of Surgery. By George Perkins, M.C., M.Ch., F.R.C.S. 236 pages, $3.00. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore, Md.: The Williams & Wilkins Co., 1954.

Historical Review of British Obstetrics and Gynaecology; 1800–1950. Edited by J. M. Munro Kerr, R. W. Johnstone, and Miles H. Phillips. 420 pages. $6.75. Edinburgh; London: E. & S. Livingstone Ltd.; Baltimore, Md.: The Williams & Wilkins Co., 1954.

Radiodiagnóstico en ginecología. tesis de doctorado. By Dr. Roberto François. 93 pages, 132 illustrations. Montevideo, Uruguay: Facultad de medicina de Montevideo, 1953.

A Stereoscopic Atlas of Human Anatomy. By David L. Bassett, M.D. Section 2—Head and Neck. Reels 35–44. Color photographs by W. B. Gruber. Portland, Oregon: Sawyer's Inc., 1954.

Intern's Manual (Cook County Hospital). By Arthur Bernstein, M.D. 292 pages. $3.00. Chicago: Year Book Publishers, Inc., 1954.